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PROGESTERONE

THE VALUE OF BASAL FAT IN THE HUMAN UTERUS AS AN INDICATOR OF OPTIMUM PROGESTERONE ACTIVITY

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THE DISTRIBUTION of lipoids in the endometrium at different phases in the human menstrual cycle was first described by Aschheim (1). He drew attention to the appearance of fat in the base of the uterine gland cells in 80% of endometria in the late second half of the cycle. Unfortunately Aschheim's findings were seriously questioned by Froboese (3) who was of the opinion that the intracellular fat in the glands was due to degenerative changes which immediately precede menstruation. On this account Aschheim's original observations failed to emerge from their academic obscurity; certainly no attempt had been made to apply these facts to clinical problems.

Gillman (4, 5) in refuting Froboese's contention that basal fat was due to cell degeneration, affirmed instead that the fat was related to progesterone metabolism. Gillman (5) found that throughout the first half and indeed in the first week of the second half of the cycle, with few exceptions, the gland cells contained no Sharlach stainable fat. In the exceptional cells the fat usually occupied a supranuclear position. Between the 19th and 25th days there was a spectacular accumulation of fat in the basal regions of the cells appearing first in the cells lying in the superficial regions of the endometrium and then spreading to the more deeply lying parts of the glands. After the 25th day the fat rapidly disappeared until the 28th day when only 10 to 20% of the cells contained basal fat. Gillman also showed that basal fat in the gland cells increased in amount in early pregnancy and decreased progressively with the age of the pregnancy. Between the 42nd and 43rd day of gestation 90% of the gland cells contained some basal fat, at 70 days 85% of cells contained some fat, whereas at 150 days only 30% of gland cells contained fat. For these and other reasons Gillman was of the opinion that the basal fat could not be regarded as a degenerative process, but instead was related to the metabolism of progesterone.

If Gillman's suggestion that basal fat in the uterine gland was related to the metabolism of progesterone could be confirmed experimentally in women then clearly a valuable technic would be made available for overcoming at least some of the many difficulties confronting us in understanding the nature of the hormonal disturbances in disorders of the menstrual cycle.

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The object of the present paper is to record the effect of estrogens and progestogens on the distribution of the lipoids in the human endometrium. In this connection opportunity will be taken of examining the endometrium in respect to its lipoids in a proven case of persistent corpus luteum associated with 18-week amenorrhea. The case was fully described by Black, Heyns and Gillman (2).

METHOD

The endometrial biopsies were made with a suction curette. In each instance large strips of endometrium were successfully obtained. The tissue was fixed in formol and Bouin. Frozen sections were made and stained with Sharlach R and counterstained with hematoxylin. In addition some of the tissue was dehydrated, embedded in wax and the sections stained with hematoxylin and eosin.

It has been desirable to describe the histological features of the endometrium in detail in order to be able to give full force to the distribution of fat in the stromal and uterine gland cells.

EXPERIMENTAL

Effect of Prolonged Administration of Estrogen in a Castrate

Case 1. A woman, aged 34, was castrated for medical reasons in September 1934. She was treated with various estrogens over a number of years. During the month of August 1940 the patient was put on 5 mg. stilbestrol daily and in September she received the same dose but on alternate days. She bled while under treatment on Oct. 3rd. From the beginning of November the patient was given stilbestrol again and while under treatment bled on Nov. 15th. A scraping was taken 4 days later. As will be appreciated from the structure of the endometrium bleeding took place from an overstimulated endometrium.

The endometrium. Under low power (×80) 3 to 4 glands per field were seen. The glands were separated by a moderately edematous stroma. The surface epithelium consisted of pear-shaped cells. They were narrow and the large, oval, vesicular nuclei containing 2 to 3 small nucleoli half filled the cell. Because of the large size of the nuclei and the narrowness of the cell, the nuclei became arranged in two layers in the epithelium.

The glands were of two types with transitional forms between them. One variety was a typical test-tube shaped gland characteristically seen in normal endometria at the height of estrus. The other was a large cystic gland. In the first type the epithelium consisted of tall columnar cells with large cigar-shaped moderately chromatic nuclei occupying at least the basal half of the cell. There were numerous mitotic figures present. In the second type the epithelium was low columnar. The nuclei were large, oval, vesicular; they were crowded; they occupied more than half of the cell. There were numerous mitotic figures present. In some glands the lumen was moderately dilated, and the nuclei in the epithelium were arranged in 2 or 3 layers.

Immediately underneath the epithelium the stroma was edematous, and the stromal cells were poorly defined, the nuclei were vesicular, round to oval. In the deeper part of the endometrium the cells were moderately well separated, and seemed to form a syncytial-like arrangement. The cells were fairly enlarged, the cytoplasm was highly vacuolated and it appeared that the edema was extra- rather than intra-cellular. Some red blood corpuscles were seen in the superficial part. Mitotic figures were present in the stromal cells.

Fat. The surface epithelium showed an occasional discrete droplet, but on the whole there was great scarcity of fat. In the glands the quantity of fat varied. In the big cystic gland there was scarcely any fat at all. In the test-tube gland there was a moderate quantity of fat which was either scattered throughout the cell or found above the nucleus in the form of 2 to 5 globules. In parts of some glands there was fat, whereas other parts contained no fat.

Almost every stromal cell in the superficial half of the endometrium contained from 1 to 5 globules of fat (fig. 1); in the deeper part of the endometrium the fat became scanty. The fat was in the form of small, discrete globules situated close to one pole of the nucleus. In about every sixth field, there were one or two cells which contained large, discrete globules, some of which had run together to form large droplets of fat.

The prolonged action of an estrogen is associated with the appearance of moderate amounts of fat in the stromal cells of the superficial half of the endometrium, and a scanty and erratic distribution of fat in the gland cells where the fat was scattered throughout the cytoplasm, although there was a distinct tendency for it to be localized in the supranuclear part of the cell.

Persistent Functional Corpus Luteum

Case 2. A patient, aged 29, had experienced amenorrhea for 18 weeks. A persistent functional corpus luteum was found in one ovary, and resected. Bleeding per vaginum for one day came on within 48 hours, and a 3-day menstrual period with profuse loss occurred 27 days after this bleeding. This patient was a nullipara and had never missed a period before. Curettage was performed at the time of the laparotomy.

The endometrium. The endometrium could be divided into a stratum compactum and a stratum spongiosum. In the compact layer the mouths of the glands were separated by stromal tissue. In the spongiosum there were large numbers of widely dilated irregular-shaped glands filled with secretion, and the walls showed definite tufting.

In the stratum compactum the stromal cells were markedly enlarged and they formed almost a continuous sheet of epitheloid cells closely applied to one another. The nuclei were large and occupied about half of the cell; they were moderately vesicular, and they contained 2 or 3 small nucleoli. Under low power the stroma looked fairly sodden and under high power it was seen that this was due to the development of a number of irregular sized vacuoles in the cell; these vacuoles may fuse. There was, in addition, a moderate amount of extracellular edema. The edema was due largely to this intracellular collection

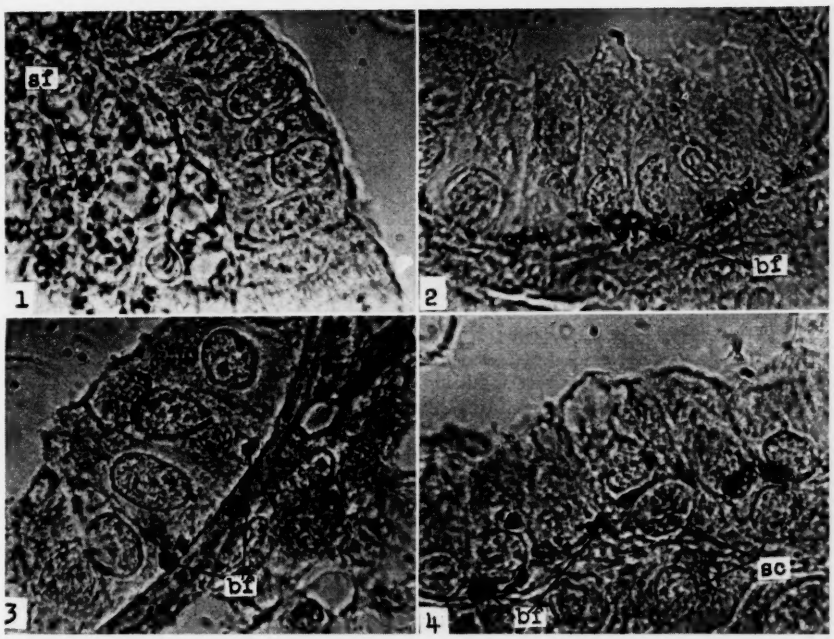

Fig. 1. Endometrium from *case 1* showing surface epithelium and stromal cells containing fat (sf). Fig. 2. Gland cells from *case 2*, showing basal fat (bf). Fig. 3. Gland cells from endometrium of first biopsy from *case 3*, showing few droplets of basal fat (bf) and edematous stroma with no fat. Fig. 4. Gland cells from endometrium of second biopsy from *case 3*, after progesterone therapy showing accumulation of basal fat (bf) and enlarged stromal cells (sc).

(All Photomicrographs of sections stained with Sharlach R and uncounter-stained. ×1022.)

of fluid. A few binucleates were present, but no mitotic figures.

In the section stained with Sharlach R it is clear that the vacuolation of the stromal cells was not due to fat, because there was far less fat than there were intracellular vacuoles. Roughly 60% of cells contained a few droplets of fat. The separation of the glands in the compactum was due chiefly to the enlargement of the stroma cells.

In the stratum spongiosum the stroma may be so highly developed as to separate the glands in some parts, but in most parts the stroma formed only a much attenuated strand of tissue separating the basement membrane of adjacent glands. The stromal cells were smaller than they were in the stratum compactum, some still being spindle-shaped.

Fat. The fat in the deeper parts of the stroma was not as abundant as in the stratum compactum, being present in about 14% of the cells. There were a few leucocytes and small round cells lying in the stroma.

The surface of the endometrium was lined by cuboidal or low columnar cells; their cytoplasm was vacuolated and some of the cells contained a few moderately enlarged globules of fat which lay either below or immediately above the nucleus. In the stratum compactum the lumen of the glands was narrow, and the lining epithelium consisted of broad low columnar cells. The nuclei were moderately chromatic, basal in position, and there were no mitotic figures present. The cytoplasm distal to the nucleus was vacuolated. One in three cells contained one or more globules of fat which was found almost exclusively below the nucleus.

In the stratum spongiosum, there was great variation in the size and shape of the cells lining the uterine glands. This was particularly accentuated on the tufts. The shape and size of the cell were determined largely by the stage in the secretory cycle in which any cell may find itself. In this preparation all stages appeared between the broad low columnar cell with basal nucleus and the large balloon cell. The ballooning of the cell was due to a physiological change which occurred in the tall columnar cell with the fairly uniformly granular cytoplasm filling the whole cell. This finely granular cytoplasm of the tall columnar cell became very clear and apparently under considerable fusion causing a marked bulging of the distal part of the cell. In many of the cells which were either of the balloon type or were in the process of becoming that type there was a number of angular basophilic bodies which were similar to those seen in Cowper's glands. When the balloon cell liberated its secretion, it reverted to the broad low columnar cell, i.e. the balloon cell and the broad low columnar cell represented two different stages in the physiological cycle of secretion of the same cell.

In most of the cells the nuclei were either just off the base or lying on the base of the cell. The shape of the

nucleus was dependent largely upon local mechanical factors, i.e. on the tufts where the cells were compressed the nuclei were mostly elongated.

Fat. One-quarter to one-third of the gland cells contained fat in the form of irregular sized droplets situated exclusively below the base of the nucleus. Sometimes these droplets had fused to form larger ones one-quarter to one-third of the size of the nucleus (fig. 2).

This endometrium showed all the characteristic features of the late second half of the cycle including the ballooned cells, and the basal fat in the epithelium of the uterine glands.

Thus in this remarkable corpus luteum which had been active for a prolonged period, the fat in the epithelial cells was restricted entirely to the infra-nuclear region; and in the stromal cells from 14% in the stratum spongiosum to 60% in the stratum compactum, contained fat. It follows, therefore, that corpus luteum activity in this natural experiment was most definitely associated with the appearance and accumulation of infra-nuclear fat in the epithelial cells. While the fat droplets in the stromal cells here were larger than those found in *case 1*, the most spectacular difference is to be found in the epithelial cells.

In view of the fact that the functional corpus luteum was associated with the accumulation of basal epithelial fat, the question arose as to whether a similar distribution of fat could be produced experimentally by the administration of progesterone.[1]

The Effect of Progesterone in the Second Half of the Cycle

Case 3. The patient was a para 1, aged 33, who complained of "flooding every month." Labor had occurred 10 years ago.

Menstrul history. She began menstruating at 14. The menstrual flow, at 28-day intervals, lasted 6 to 7 days. For the last 3 or 4 years the menstrual flow, at 26-day intervals, lasted 8 to 10 days. Even as a girl she always lost a lot of blood, but this is much worse now and large clots are present, causing much pain. She is quite exhausted after the period. Examination revealed nothing of note, and a uterine sound passed only 2½". The menses on May 30, 1940 lasted 8 days with a profuse flow. The first biopsy and curettage was on June 24th, the 27th day of the cycle. The menses on July 27th was accompanied by very severe loss of blood. Injections of proluton, 5 mg. each, were administered on days 18, 20, 22 and 24 of this cycle. The second biopsy and curettage was on 25th day of the cycle.

First biopsy. The endometrium was incompletely differentiated into a stratum compactum and a stratum spongiosum. Under low power (×80) an average of 6 to 10 glands per field could be seen. The glands were moderately dilated in their middle and deeper parts. The upper part of the neck and the mouth were narrow. The glands were irregularly dilated and in a few there was evidence of tufting. Under high power (×900) the cells varied in height; some were low columnar, others were very tall but broad columnar cells, depending entirely on the stage they may have attained in the secretory cycle. The side walls of the cells were sharply defined. Except on the tufts the nuclei were applied close to the base or were slightly removed from the base of the cell; they were round or oval, vesicular and contained 2 to 3 small but prominent nucleoli. On the tuft the nuclei were situated near the free margin of the cell or near the base. In the more dilated glands the epithelium was almost cuboidal. There were no mitotic figures in the gland cells. The stroma cells in the superficial part of the endometrium were separated widely by an intense edema. In the deeper part the cells were more compact due to a less intense edema. The cell margins were poorly defined; the nuclei were large, oval, very vesicular and contained 3 to 4 prominent nucleoli plastered against the nuclear membrane. In the deeper part of the endometrium the cells were much more compact and the nuclei were oval to spindle shaped. Polymorph and round cells were present in the stroma. There were some mitotic figures in the stroma and there was a mitotic figure in an endothelial cell.

Fat. There was no fat present in the majority of the glands, but in a few cells there was basal fat in the form of fine globules situated at the base of the cell (fig. 3). In 60 to 70% of the stroma cells there was fat in the form of one or more globules arranged near one or both poles of the nucleus.

Second biopsy. (After 20 mg. progesterone.) The endometrium was definitely differentiated into a stratum compactum and a stratum spongiosum. Under low power (×80) 6 glands per field could be seen. The glands were moderately dilated in their middle parts. The upper part of the neck and mouth were narrow. There was marked tufting in some of the glands.

Under high power (×900) the gland cells varied from a tall columnar to a low, broad columnar. The distal poles of the cells were clear and bulging. The side walls of the cells were very sharply defined. The nuclei were round to oval, more chromatic than in the previous specimen, and were found almost exclusively near the base of the cell, except in the tufts; the nucleoli were small but prominent. There were some binucleate cells.

There was a very good stromal reaction throughout the superficial half of the endometrium such as found characteristically in the normal premenstruum. The cells were enlarged, the cell walls clearly seen; the nuclei were either extremely large, round or oval, vesicular, with prominent nucleoli, or they were hyperchromatic, small and with wrinkled membrane. The cytoplasm in some of the cells was faintly basophilic, in others faintly eosinophilic and showed a moderate degree of vacuolation. There was some edema present. Polymorph and round cells were present, and mitotic figures were common.

Fat. Almost every single epithelial cell of the tall columnar variety contained some basal fat (fig. 4). But those which had completed their secretory cycle, particularly the broad cuboidal ones, contained either no fat or only a few small globules. The fat was very scanty in the stromal cells in the superficial regions although some cells contained one or two droplets. Deeper down in the stroma there was no fat.

[1] Progesterone, in the form of Proluton, was obtained from the Schering Corporation.

Thus we see that in the first biopsy specimen there was definite evidence of progesterone activity, but not as marked as described by Gillman in the corresponding stage of the normal cycle. Although fat was present in the base of the epithelial cells, it was not abundant and only occurred in some cells. The majority of stromal cells, particularly in the superficial part, contained some fat droplets. On the other hand, in the endometrium taken at the same time of the cycle after progesterone therapy not only was there a gross microscopic change where the endometrium was definitely demarcated into a stratum compactum and stratum spongiosum, but there was also a remarkable increase in the epithelial fat. Almost every epithelial cell of the tall columnar variety contained moderate numbers of almost uniformly sized fat droplets, exclusively restricted to the infranuclear region of the cell. Even in the stromal cells, although there was some fat present in the superficial part of the endometrium it was diminished as compared with the first specimen.

Two important points emerge from this experiment. Firstly, where an endometrium which, when examined by ordinary histological technics, does not show a well developed late premenstrual reaction, the number of epithelial cells showing the presence of basal fat is very low. Secondly, if progesterone is given in the second half of the cycle in quantities such as we have used, the cells containing basal fat become enormously increased in number. In the latter instance progesterone actually produced a well-developed premenstrual type of endometrium. The appearance of the basal fat and the premenstrual type of endometrium developed after progesterone therapy further corroborates our original contention that the first endometrium showed a deficiency of progesterone.

The Effect of Progesterone in the First Half of the Cycle

In *case 3* progesterone was administered in the second half of the cycle. The question naturally arose as to whether the appearance of basal fat was due to the action of progesterone per se or whether progesterone produced this effect only when conditions in the endometrium were comparable to those normally occurring in the late second half of the cycle. In order to elucidate this point further, progesterone was administered in the first half of the cycle.

Case 4. A para 3, aged 35, complained of severe bleeding at the periods. The last labor was 4 years ago.

Menstrual history. She began menstruating at 14. Menstrual periods have never been regular, sometimes there has been a 2-month amenorrhea. Periods have become more frequent and she now is free from bleeding for intervals of only 7 to 14 days. The menses on September 18, 1940 were profuse for the first 3 days. The first biopsy was on October 3rd, the 15th day of the cycle. The menses which began on October 7th lasted until October 14th. Proluton in 5 mg. doses were given on the 15th, 17th, 19th, 21st, and 23rd of October, 1940, i.e. between 8th and 16th days of cycle. The second biopsy was on October 24th, the 17th day of the cycle.

First biopsy. Under low power (×80) the endometrium appeared to be very thick and there were 8 to 10 glands per field, closely applied to one another and separated by thin bands of stroma.

The surface epithelium consisted of low columnar, even cuboidal, cells with the nuclei arranged in some places in two levels in the epithelium. The glands were moderately dilated, regular in outline. The nature of the epithelium varied considerably. In some glands the epithelium was of the tall columnar variety with finely granular cytoplasm and large vacuoles occupying the basal third of the cell. Some of these vacuoles actually indented the lower pole of the nucleus. The nuclei of these cells were broad oval to cigar-shaped, and they occupied the middle half of the cell; they were vesicular and contained 2 or 3 nucleoli. In other glands the cells were columnar; the cytoplasm was finely granular and eosinophilic, and the much elongated broad vesicular nucleus almost filled the cell. In other glands the cells were tall columnar with a ballooned free margin projecting into the lumen of the gland. These cells were broad and their side walls were very sharply defined. The nucleus was oval or almost spherical in shape, the nuclear membrane was slightly wrinkled, and there were 3 to 4 fairly prominent nucleoli. All the nuclei were situated close to the base of the cell. There were no mitotic figures to be seen in any of the gland cells.

There was a moderate amount of edema in the superficial part of the endometrium, the stromal cells being fairly widely separated; the nuclei were polymorphous, some being large, oval, round and vesicular, whereas others had irregular nuclear membranes and were hyperchromatic. Between some glands the stromal cells were spindle-shaped and reduced in numbers; between other glands there was a moderate abundance of stromal cells the nuclei of which were round or oval and moderately vesicular. There was no mitosis in the stromal cells. There were in addition a number of round cells.

Fat. In the glands, with very rare exceptions, there was no fat at all in any of the epithelial cells either above or below the nucleus. In the very exceptional cases there were either one or two globules of fat situated below the nucleus. The infra-nuclear vacuolation was not due to fat. In the edematous part of the stroma almost every cell contained one or more globules which reach up to 1–2μ in diameter. In the deeper part of the stroma, particularly where the edema was less marked, because the stroma was more compressed and the cells contained 1 to 3 very small droplets of fat, there appeared to be much less fat.

Second biopsy after 25 mg. of progesterone. Under low power (×80) there were 5 to 6 glands per field separated by a moderate amount of stroma which was moderately edematous, particularly below the surface epithelium and extending to the upper part of the glands.

The cells of the surface epithelium were moderately

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tall columnar in shape. The nuclei were round to oval and were arranged in two layers in the epithelium.

The glands differed very considerably in their neck, mid and lower regions. In the neck region near the mouth of the gland there were tall columnar cells; the cytoplasm in the supra-nuclear region was finely granular and eosinophilic, the infra-nuclear region which is about one-third of the height of the cell was occupied by one large vacuole apparently under tension. The broad oval, vesicular nucleus, with 3 to 6 nucleoli plastered against the nuclear membrane was situated in the middle third of the cell. In some cells in this region even the supranuclear part had become clear and occupied by small, irregularly shaped and sized vacuoles, many of which had fused and gave a clear appearance even to the supranuclear region.

In the middle part of the gland the lumen was irregular and there was some obtuse tufting of the epithelium. The cells were moderately tall and columnar, the cytoplasm was granular throughout the cell; there was considerable variation in the size and shape of the nuclei, some of which were elongated, some were fairly broad and occupying three-quarters of the cell, whereas others were large, round and vesicular and occupied the basal half of the cell. There were all transitional forms between these types of nuclei.

Towards the fundal region of the gland the tall columnar cells were very narrow. The very elongated narrow nucleus seemed to occupy almost the whole width of the cell. Therefore there seemed to be a crowding of the nuclei in the epithelium. They were, however, all arranged at one level. The nucleus occupied three-quarters or more of the height of the cell.

In the superficial part of the endometrium there was a moderate amount of edema in the stroma which separated the stromal cells. The nuclei of these cells were round, or very broad oval, vesicular, and it was very difficult to see any cytoplasm surrounding these nuclei. In the deeper part there was less edema and there was a great variation in the character of the stromal cells. Some were much elongated, others broad oval, and still others round. Some of the nuclei were hyperchromatic, small, with wrinkled nuclear membrane. In some parts there were considerable quantities of stroma separating the glands, and in others the stroma was very thin.

There were some mitotic figures in the stromal cells but none in the gland cells.

Fat. In the gland cells there was no fat whatsoever. In the stromal cells in the edematous zone the fat droplets were small and there were very few per cell; consequently the fat seemed to be very scanty. In the deeper parts of the endometrium there was scarcely any fat at all.

In comparing these two endometria—one without, and the other after, progesterone treatment in the first part of the cycle—there is no question but that there was a difference in their structure; histologically they were not similar. In the endometrium treated with progesterone the glands and the stroma both showed the effect of corpus luteum activity. In both endometria, however, there was no basal fat in the gland cells, but there was perhaps a diminution of fat in the stromal cells of the endometrium treated with progesterone. We are not prepared to say at this stage whether the reduction in the stromal fat can be regarded as significant.

The important point that emerges from this experiment is that progesterone when given in the first part of the cycle cannot cause the appearance of basal fat in the uterine glands.

DISCUSSION

In the castrated woman (*case 1*) the prolonged administration of estrogen, although it did cause the appearance of stromal fat, was ineffective in producing basal fat in the gland cells.

In *case 4* progesterone given early in the first half of the cycle also did not cause the appearance of basal fat. There is little doubt, from what we know of the normal cycle, that the estrogen produced by the subject's own ovaries before the beginning of the experiment was inadequate, and also had not acted for a sufficient length of time on the endometrium to allow for optimum action of progesterone. It may be possible, however, that, coupled with the fact that the endometrium had been inadequately prepared by estrogen, the amount of progesterone and the time over which it acted was also not optimal; and, therefore, that the optimum balance between the estrogen and progestogen had not been achieved for the required effect to be produced.

In *case 3*, giving progesterone in the second half of the cycle to a woman who had exhibited basal fat only in some epithelial cells in a previous cycle caused the appearance of fat in almost all the gland cells. The length of time over which estrogen and progesterone, spontaneously produced by the subject, had acted in this case can most probably be regarded as normal, because she had a regular cycle and she had actually produced some degree of luteinization of the endometrium.

The other factors which may have prevented her from spontaneously developing a normal premenstrual endometrium may have been associated with disturbances in the production of the actual amounts, or optimum proportions, of estrogen and progestogen. Estrogen may have been insufficient or excessive; progesterone may have been insufficient or excessive; and the balance between the two may have been disturbed so as to prevent full development of the endometrium. The administration of 20 mg. of progesterone in the second half of the cycle produced a full-grown premenstrual endometrium associated also with the appearance of fat in the base of almost all gland cells. This indicates that the addition of progesterone adjusted the balance, thus bringing about an optimum effect. In this case, therefore, it is possible that an excess of estrogen may have upset

the requisite balance, and may have interfered with the appearance of basal fat. Therefore, progesterone in this case was obviously the critical factor in exciting the production of basal fat.

In the persistent functional corpus luteum associated with prolonged amenorrhea, almost all the cells in the glands of the endometrium contained basal fat. The minute structure of the corpus luteum revealed that it was in a state of great functional activity. It can scarcely be fortuitous that an active corpus luteum, in this case as in pregnancy, should occur simultaneously with such selective localization of fat in the gland cells.

From the foregoing, it seems reasonable to presume that there is a causal relationship between progesterone functioning under optimum conditions and the consistent appearance of basal fat. It does not seem presumptious even on the basis of this selected but limited number of experiments in women to recommend the use of basal fat in the uterine gland cells as an indicator of optimum progesterone activity.

SUMMARY

The effects of estrogen on the lipoids in the human endometrium have been examined. Prolonged administration of estrogen in a castrated woman causes the appearance of fat in the stromal cells and fat in some of the uterine gland cells, but in the latter instance the fat tends to be found in the supranuclear region of the cell.

In persistent functional corpus luteum fat is present in the stromal cells but in the uterine gland cells the fat is almost exclusively basal in position.

Where the corpus luteum does not function optimally the basal fat is only found in some gland cells on the 25th day of the cycle. The giving of progesterone in the second half of the cycle to such a case causes the appearance of basal fat in almost all the gland cells lying in the stratum compactum and also in the glands in the superficial regions of the stratum spongiosum.

Progesterone administered to women in the first part of the cycle does not produce basal fat in the uterine gland cells.

It is concluded that progesterone alone will not lead to the appearance of basal fat, but that basal fat cannot appear in the absence of progesterone. An optimum balance between estrogen and progestogen seems to be necessary before basal fat can be formed in the uterine gland cells.

It is recommended that the examination of human endometria for basal fat may afford some additional information concerning the metabolism of progestogens.

We wish to acknowledge our deep appreciation to Miss Christine Gilbert of the Anatomy Department for technical assistance in the preparation of sections and the photomicrographs. Our thanks are also due to Dr. C. Kark for permission to use data relating to *case* 1. This investigation was assisted by a grant made by the National Research Grant Board of South Africa.

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VALUE OF PREGNENINOLONE IN THE TREATMENT OF FUNCTIONAL UTERINE BLEEDING

THERAPY OF FUNCTIONAL BLEEDING

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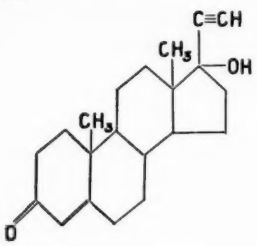
GOOD CLINICAL RESULTS with testosterone propionate in the treatment of functional uterine bleeding have been reported from several clinics during the past 3 years (1–9). It has, however, been found by a number of investigators that the administration of this hormone resulted in the appearance of arrhenomimetic phenomena (hirsuties, hoarseness, enlargement of the clitoris) (3, 8–11). Our studies have shown that these unpleasant side-effects occur infrequently if the therapeutic dose does not exceed 300 mg. per month and if certain precautions are taken in selection of cases and the hormone administration is controlled with vaginal smears (11, 12). However, the necessity for employing these precautions detracts somewhat from the value of this form of therapy. For this reason, we attempted to find some other androgen which might possess the therapeutic properties of testosterone propionate without inducing arrhenomimetic effects. During the course of this investigation, the endocrinologic properties of a number of compounds related structurally to testosterone have been studied.

Here we wish to report the results of our studies in the treatment of functional uterine bleeding with pregneninolone.



This compound is a sterol which is closely related to both testosterone and progesterone and was synthesized by Inhoffen, Longemann and Serini (13). It has been described as Δ^4 pregnen-in-20-on-3-ol-17; ethinyl testosterone; anhydro-hydroxy-progesterone and pregneninolone. Its androgenic potency is very low. Emmens and Parkes (15) have reported its androgenic activity as approximately 1/600 that of testosterone. The compound, unfortunately, is only slightly soluble in oil. For this reason, it was not feasible to administer, parenterally, amounts comparable to testosterone propionate. However, it has been shown that the compound is absorbed in effective amounts from the intestinal tract in animals (13, 14, 15) and women (16, 17) and that it has a strong progestomimetic and a weak estromimetic action in animals (15, 18) and women (16, 17). In amounts up to 10,480 mg., over periods extending up to 20 months, it has induced no arrhenomimetic effects (17).

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MATERIAL AND METHODS

A group of 14 women with functional menorrhagia of 1 to 10 years duration were selected for this study. Studies were made of vaginal smears and endometrial and vaginal biopsies taken before and after treatment to correlate the therapeutic and morphologic effects of the hormone. Pre-menstraul endometrial biopsies, taken before institution of therapy, revealed a typical secretory phase in all but 2 cases in which proliferative patterns were found.

Dosage. Pregneninolone[1] was taken orally, in 10 mg. doses, 3 times daily, over periods varying from 19 to 116 days. The smallest quantity administered was 570 mg., during 19 days, and the largest, 3480 mg., over a period of 116 days. The details of dosage are given in table 1.

[1] The pregneninolone, in the form of Pranone, used in this investigation, was supplied by the Schering Corporation, Bloomfield, N. J., through the courtesy of Dr. Erwin Schwenk.

TABLE 1. DOSAGE OF PREGNENINOLONE IN THE TREATMENT OF FUNCTIONAL UTERINE BLEEDING

Case No.	Total Pregneninolone Dosage	Period of Administration
	mg.	*days*
1	570	19
2	750	25
3	840	28
4	1290	43
5	1320	44
6	1650	55
7	1800	60
8	1920	64
9	1980	66
10	2340	78
11	2460	82
12	2580	86
13	3180	106
14	3480	116

RESULTS

Clinical studies. Nine of the 14 cases of menorrhagia showed no change in the frequency, duration or extent of bleeding. Three patients stated that they had noted a slight decrease in the quantity of menstrual flow. One woman became pregnant 6 weeks after the onset of therapy. Another, 43 years of age, acquired amenorrhea for 3 months, followed by a return of the menorrhagia.

Morphologic studies. No androgenic effects were noted in either the vaginal smears or endometrial and vaginal biopsies. The 2 cases with anovulatory bleeding continued to manifest proliferative endometrial pictures pre-menstrually, while all the others showed typical secretory patterns.

DISCUSSION

It is apparent from the results reported here that pregneninolone can hardly qualify as a therapeutic androgen to substitute for testosterone propionate. The therapeutic results in this series were essentially negative. It is noteworthy that in no case were any androgenic effects observed, such as occur following large doses of testosterone propionate, viz., suppression of menstruation associated with inhibitory effects in the endometrium and estrogen deficiency signs in the vaginal smears. In no case did arrhenomimetic effects (hirsuties, hoarseness, enlargement of the clitoris) occur. The absence of any therapeutic effect on the bleeding is probably attributable to the failure of pregneninolone to manifest androgenic potency in the human female. Hamblen et al. (19), have reported good results (maintenance of normal cyclic bleeding during treatment) by means of oral therapy consisting of estradiol followed by estriol glucuronide and pregneninolone. This therapy was instituted in these patients after primary control of the meno-metrorrhagia by either curettage or injections of estrogens and progesterone. Because of the variety of therapeutic factors employed, it is difficult to evaluate the role played by pregneninolone in the therapeutic effect obtained by these investigators.

Cohen and Stein (20) have reported the treatment of a series of 25 cases of functional meno-metrorrhagia with daily doses of pregneninolone varying from 15 to 30 mg. The authors concluded that pregneninolone proved effective in 12 of the 25 patients, but made the observation that "the improvement was temporary unless treatment was continued for several months." The duration of the therapeutic effect after the discontinuation of the pregneninolone was not stated.

SUMMARY

A group of 14 cases of functional uterine bleeding was treated with pregneninolone and the therapy followed with morphologic studies of the endometrium and vaginal smears.

The dose used was 30 mg. per day. The total doses administered varied from 570 to 3480 mg., during periods varying from 19 to 116 days.

Only 3 cases appeared to be slightly improved during the period of treatment.

In the dosage employed, pregneninolone had no suppressive effect on the menstrual cycle, produced no anti-gynecogenic effects on the endometrium and vaginal mucosa, and had no arrhenomimetic action.

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ETHINYL ESTRADIOL

THERAPEUTIC EFFECTIVENESS OF ORALLY ADMINISTERED ETHINYL ESTRADIOL

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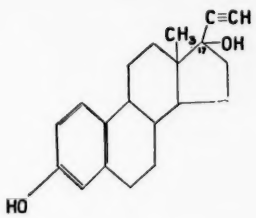
IT HAS BECOME increasingly more evident during the past 5 years that treatment of the menopause syndrome with estrogens is a form of substitution therapy, the need for which is perpetuated by the very administration of the hormone. Once the patient has been relieved of the distressing menopause symptoms, we have to face the problem of maintaining the therapeutic effect. Discontinuation of therapy is almost invariably followed by a recurrence of symptoms. The patient consequently requires a constant supply of estrogens to meet her physiologic needs.

To be ideal, maintenance therapy should be easily administered by the patient herself, preferably orally. In addition, because of the probability that the hormone would have to be taken for many months or years, its administration should be completely devoid of any unpleasant reactions or potential harm. Maintenance therapy should, furthermore, be inexpensive. Alpha-estradiol fulfills the first two requirements, but fails to meet the third. For, although it is effective when administered orally, it loses approximately 90% of its estrogenic activity when absorbed through the intestinal tract. For this reason, in order to obtain a therapeutic effect, it is necessary to administer comparatively huge doses, making this, otherwise ideal estrogen, too costly for general use. The synthetic estrogen, stilbestrol, is highly active when taken by mouth and is very inexpensive but, unfortunately, induces vomiting or nausea (the incidence ranging up to 80% according to some reports) (1–6) too frequently to permit of its acceptance as the perfect estrogen for maintenance therapy. In our search for an orally active estrogen, we undertook to study the clinical effectiveness of ethinyl estradiol.

This compound was prepared by Inhoffen and Hohlweg (7) by the replacement of the 17th carbon atom in estradiol by an ethinyl group. These authors report that, when given subcutaneously in oil, ethinyl estradiol and estradiol are equal in potency but, when given orally, ethinyl estradiol is 15 to 20



times as active as estradiol. Clauberg and Ustun (8) reported the use of ethinyl estradiol in secondary amenorrhea and oligomenorrhea and demonstrated proliferative changes in the uterine mucosa following doses of 56 mg. of ethinyl estradiol, given over a period of 20 days. No symptoms of toxicity were reported in their series of 6 cases.

MATERIALS AND PROCEDURE

A total number of 27 patients was treated. Included in this study were 12 patients in the natural menopause, 12 surgical castrates and 3 x-ray castrates. The patients had characteristic menopausal symptoms: flushes, nervousness, insomnia, gastrointestinal disturbances, vertigo, headache and arthalgias. All patients were submitted to complete physical examination. Vaginal smear and biopsy studies were performed in order to determine, objectively, the presence of an estrogen deficiency and to evaluate the estrogenic action of the hormone used. The aqueous fuchsin technic for staining vaginal smears was employed (9, 10). The hormone was administered in the form of enteric coated tablets containing 0.15 mg.

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[1] Joseph Brettauer Fellow in Gynecology.

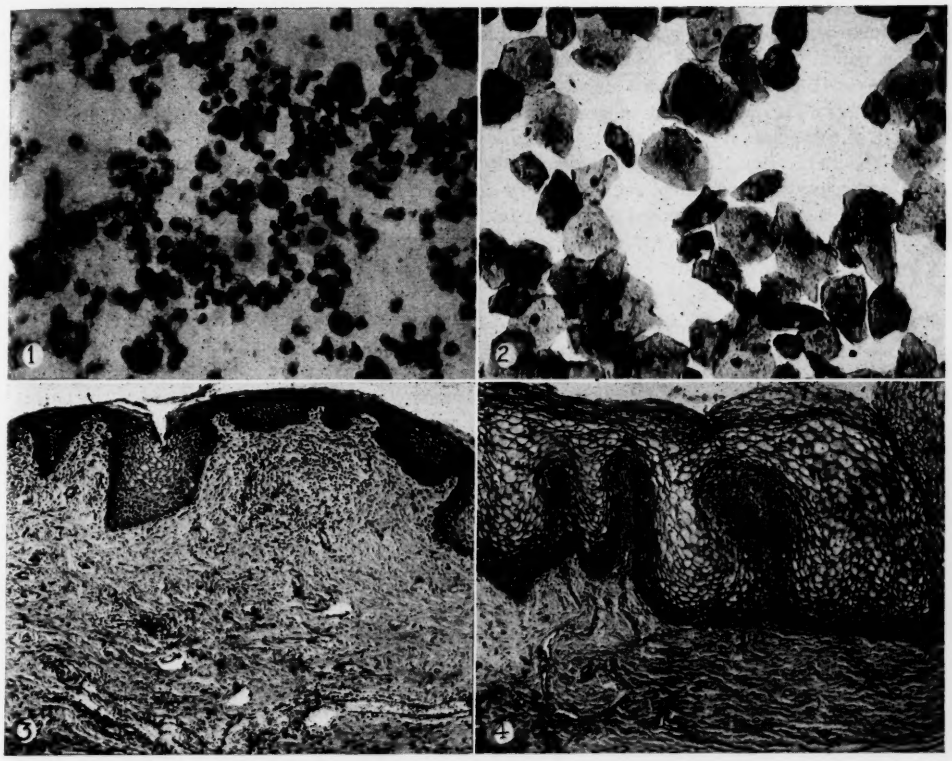

Fig. 1. *Case S.K.* Age 31; x-ray castrate (3 years). Preliminary vaginal smear showing marked estrogen deficiency. Note presence of leukocytes, and round epithelial cells with large nuclei, ('atrophy' cells) (×128). Fig. 2. *Case S.K.* Vaginal smear following the administration of 3.15 mg. of ethinyl estradiol (in tablets) over period of 7 days. Note disappearance of 'atrophy' cells and leukocytes, clean appearance of the smear and large squamous cells with small nuclei (×180). Fig. 3. *Case J.F.* Age 56, surgical castrate (11 years). Preliminary vaginal biopsy showing moderate degree of estrogen deficiency. Note thin mucosa, no cornification; almost complete disappearance of vacuolated zone with inactive basalis, subepithelial leukocytic infiltration (×64). Fig. 4. *Case J.F.* Vaginal biopsy following the administration of 30.6 mg. of ethinyl estradiol (in tablets) over period of 34 days. Note increased thickness of mucosa with well demarcated cornified and vacuolated zones, absence of subepithelial leukocytes and well-defined basalis (×64).

of ethinyl estradiol and in an alcoholic solution containing 3.75 mg. per 100 cc. (4 cc. = 0.15 mg. of ethinyl estradiol).

Results with ethinyl estradiol tablets. Twenty-one patients were treated with the ethinyl estradiol tablets. Satisfactory clinical relief of symptoms was noted within 4 to 7 days, on an average daily dose of 0.45 mg. (= total dose of 1.8 to 3.15 mg.). Some patients were satisfactorily maintained thereafter on 0.15 mg. daily; others required 0.3 mg. daily.

Estrogenic effect on vaginal mucosa. Vaginal smear and biopsy studies revealed a definite estrogen effect which paralleled the symptomatic improvement. At the end of 5 to 7 days, following an average daily dose of 0.45 mg., the 'atrophy' vaginal epithelial cells and leukocytes in the vaginal smears were replaced by large squamous epithelial cells with small nuclei. Paralleling these changes, the narrow atrophic vaginal mucosa became converted into a thick mucous membrane, exhibiting a well-defined cornified zone and a thick vacuolated zone with an active basalis (fig. 1–4). The vaginal smears of the 2 patients who obtained no symptomatic relief from ethinyl estradiol showed no estrogenic effects. Uterine bleeding occurred in only 1 patient, after a total dosage of 23.1 mg., given over a period of 50 days. The bleeding began 2 weeks after discontinuation of therapy and persisted for 5 days.

Gastric symptoms. Four patients developed symptoms which necessitated discontinuation of the therapy. These symptoms were nausea, vomiting, abdominal pain and malaise, which promptly subsided on discontinuation of therapy. These symptoms were induced with as little as 0.3 mg. of ethinyl estradiol. Three other patients had similar manifestations of intolerance, which disappeared on reduced dosage.

Results with ethinyl estradiol in alcoholic solution. Five patients were given the alcoholic solution of ethinyl estradiol. In 4 of the 5 patients, the symptoms were partially relieved after 0.9 mg. to 1.5 mg. of the hormone. The development of gastric symptoms in all of these cases necessitated the discontinuation of the medication. The predominating complaints were nausea and vomiting, even after 1 or 2 doses. Among the other effects noted were epigastric pain, chills and vertigo. It is interesting to note that 3 of these patients subsequently were given enteric coated tablets of ethinyl estradiol and promptly developed similar symptoms.

DISCUSSION

In a study to be reported, we attempted to compare the oral effectiveness of estradiol and ethinyl estradiol in women. The latter substance appeared to be approximately 10 to 20 times more effective, therapeutically, than the former. It is apparent from the study reported here that ethinyl estradiol is highly potent when administered orally and is capable of relieving menopausal symptoms and inducing typical estrogenic effects in the human vaginal mucosa. Because of its potency, this compound may fill the need for an orally active estrogen. But, until the cause of the nausea and vomiting is ascertained and corrected, it cannot be recommended for clinical use. Further studies are being conducted with this objective in view.

SUMMARY

Ethinyl estradiol in the form of enteric coated tablets and in alcoholic solution was administered, orally, to 27 patients (tablets, 22 patients; alcoholic solution, 5 patients) with menopausal symptoms and morphologic evidence of estrogen deficiency.

Ethinyl estradiol in the form of enteric coated tablets has been found to possess high estrogenic potency when administered orally. Its effectiveness was demonstrated by the relief of menopausal symptoms and by the characteristic estrogenic changes induced in the vaginal mucosa.

Nausea and vomiting occurred in 4 of the 22 patients taking the enteric coated tablets and in all 5 patients taking the alcoholic solution of the hormone.

Because of the therapeutic effectiveness of ethinyl estradiol in small doses, this compound holds forth promise of supplying the answer to the problem of finding an orally active physiologic estrogen.

In spite of the demonstration of its high estrogenic potency, approval of ethinyl estradiol for clinical use must be withheld until the cause of the nausea and vomiting has been determined and eliminated.

The ethinyl estradiol used in this investigation was supplied by the Schering Corporation, Bloomfield, N. J., through the courtesy of Drs. Erwin Schwenk and Max Gilbert.

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ESTROGEN THERAPY

A COMPARISON OF THE CLINICAL EFFECTIVENESS OF ESTRADIOL DIPROPIONATE AND ESTRADIOL BENZOATE

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ESTRADIOL DIPROPIONATE has an apparent superiority over other parenteral estrogens in the treatment of menopausal symptoms. It will relieve and maintain patients symptom free with treatment once a week or, in the majority of cases, with treatment every two or three weeks (1, 2). Estrone is relatively inefficient in that it is less potent and must be administered much more frequently. A direct comparison of the two substances in a group of patients demonstrated that estradiol dipropionate was the more effective of the two (2).

In the experimental animal estradiol dipropionate also has a more prolonged action than equal amounts of estradiol benzoate (3). There has been, to the author's knowledge, no direct comparison of these two substances in the human being. It was thought, therefore, that the following data on this subject should be of interest.

METHODS

The 11 menopausal females used in this study were believed to be receiving the minimal dose of estradiol dipropionate necessary for the maintenance of symptomatic relief. These patients were having no hot flashes or a total of 2 to 5 mild ones during the course of a week, but were otherwise comfortable. All had been under treatment for at least 6 months, and all had been maintained on a constant dosage level and treatment frequency for at least 9 weeks. Without the patient's knowledge, estradiol benzoate was substituted for the estradiol dipropionate at the same dosage level and treatment frequency.

At each clinic visit the patients were interviewed, the number of hot flashes and other symptoms recorded and vaginal smears were made.

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RESULTS

The number of hot flashes per day and the state of the vaginal smear are presented in figure 1. The character of the smear is represented by a numerical value according to a system previously outlined (2). The value "4" refers to a fully cornified (estrogenic) smear and "0" refers to the completely atrophic (senile) smear.

Following the substitution of estradiol benzoate for estradiol dipropionate, hot flashes appeared or were increased in number in 9 of the 11 patients. The appearance or increase in number of hot flashes tended to occur after the first administration of estradiol benzoate in those patients requiring weekly treatment with estradiol dipropionate. In some of the patients maintained by treatment every 2 or 3 weeks, the number of flashes was not definitely increased until after the second administration of estradiol benzoate.

In 6 of these 9 patients the appearance or increase in the number of flashes seemed definitely significant (*Pt.* 1, 2, 5, 6, 7, and 9) and was associated with reappearance of other menopausal symptoms in 5 of them. In 2 patients the increase in number of flashes per week was less marked, but was associated with reappearance of other symptoms (*Pt.* 3 and 10).

In 3 patients (*Pt.* 1, 2 and 4) there were definite regressions in the state of the vaginal smear. One of these (*Pt.* 4), had no increase in the number of flashes associated with this regression. Another patient (*Pt.* 3) showed some regression, but since the smear had shown little evidence of stimulation at the beginning of the test period this regression, in itself, cannot be considered significant. In the remaining cases there was no change in the status of the smear.

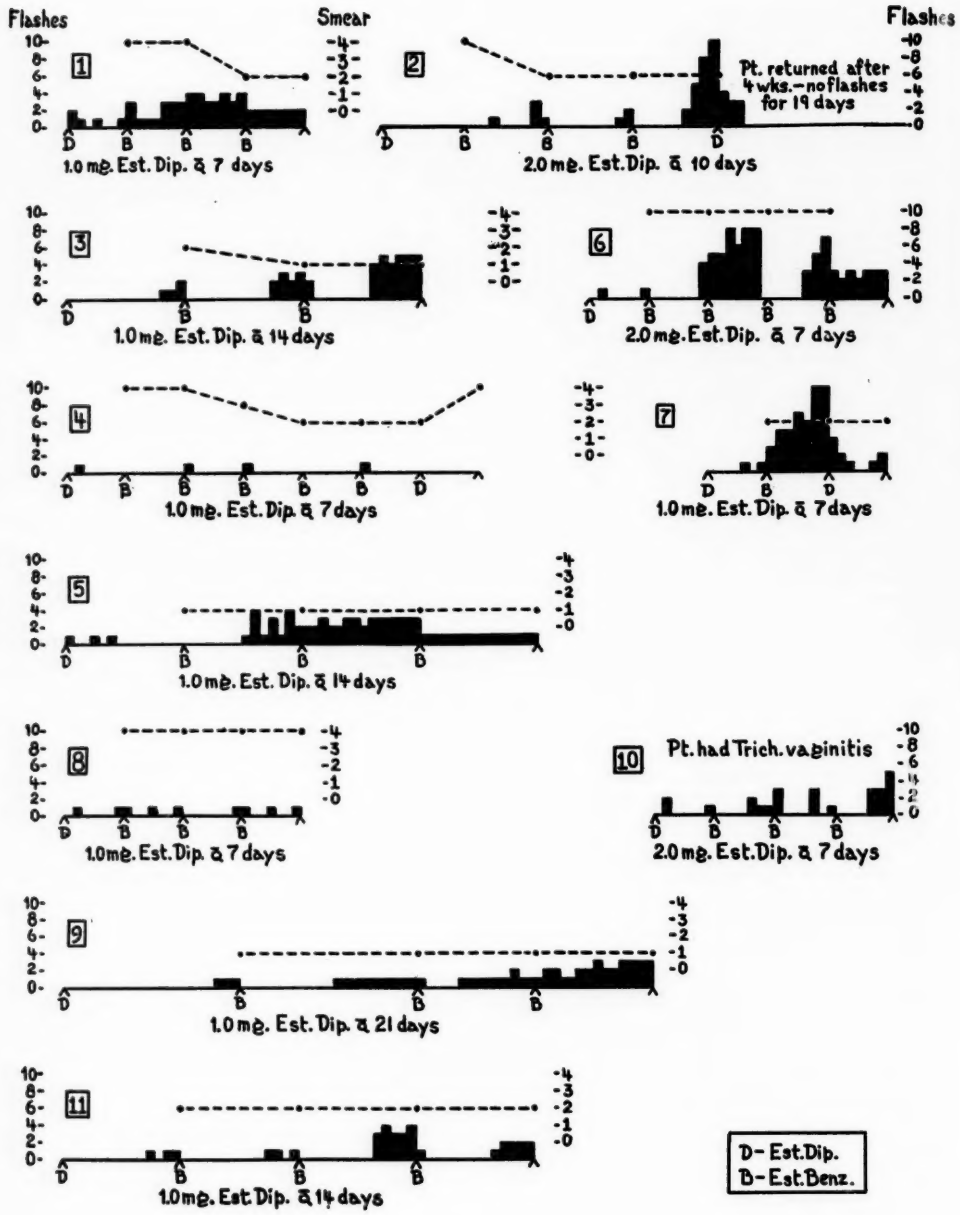
Flashes
Smear
Flashes
1
2
Pt. returned after 4 wks.—no flashes for 19 days
1.0 mg. Est. Dip. q 7 days
2.0 mg. Est. Dip. q 10 days
3
6
1.0 mg. Est. Dip. q 14 days
2.0 mg. Est. Dip. q 7 days
4
7
1.0 mg. Est. Dip. q 7 days
1.0 mg. Est. Dip. q 7 days
5
1.0 mg. Est. Dip. q 14 days
8
10
Pt. had Trich. vaginitis
1.0 mg. Est. Dip. q 7 days
2.0 mg. Est. Dip. q 7 days
9
1.0 mg. Est. Dip. q 21 days
11
1.0 mg. Est. Dip. q 14 days
D - Est. Dip.
B - Est. Benz.

FIG. 1

DISCUSSION

Others have observed inconsistencies between the dosage level required to cornify the vaginal mucosa and that necessary to control menopausal symptoms. This lack of correlation between the dosage levels necessary for these effects is well demonstrated in the present series. In 5 of these 11 patients the symptoms were controlled under the influence of estradiol dipropionate, but the vaginal smear showed little or no stimulation. With the substituted estradiol benzoate one patient (*Pt. 6*) maintained a fully cornified smear, but had a recurrence of symptoms. Another patient (*Pt. 4*) showed a definite regression in the vaginal smear findings, but her symptoms remained comfortably unchanged during the 5 weeks of estradiol benzoate administration.

The author realizes that symptoms in the menopausal patient can be intensified or diminished by factors other than administered estrogens. Sedatives will diminish and, in an occasional patient, completely control these symptoms. Environmental stress, such as financial worries or psychic trauma, may intensify them. Sedatives, however, were not given to any of these particular patients. It is possible that increased environmental stress may have occurred concomitant with the administration of estradiol benzoate and caused the recurrence of symptoms in one or two patients. It seems unlikely, however, that this could have occurred in all 9 of the patients which showed recurrence of symptoms. It seems more likely that the recurrence of symptoms was due to the lesser effectiveness of the estradiol benzoate.

The evidence demonstrates then that estradiol dipropionate is more effective than estradiol benzoate in controlling menopausal symptoms. A greater effect of the estradiol dipropionate on the state of the vaginal mucosa is not so strikingly shown by the data. This is due to the fact that half of the patients showed little or no stimulation of the vaginal mucosa when under treatment with estradiol dipropionate, and therefore could hardly be expected to show much less stimulation with the benzoate. None of the patients showed any greater stimulation with the estradiol benzoate. In patients such as these, however, one is treating the menopausal symptoms and not the vaginal mucosa. As variable as they may be, the response of the menopausal symptoms are the true criteria of the effectiveness of estrogens and their effects on vaginal smears are only of secondary interest and importance.

SUMMARY

The data show that the substitution of estradiol benzoate for estradiol dipropionate caused a regression in the vaginal smear in 3, and a recurrence of symptoms in 9 of 11 patients. It therefore seems apparent that estradiol benzoate is clinically less effective, mg. for mg., than estradiol dipropionate.

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THERAPY OF FUNCTIONAL BLEEDING

USE OF TESTOSTERONE PROPIONATE IN FUNCTIONAL BLEEDING

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IN THE PAST THREE YEARS testosterone propionate has been used extensively in the treatment of functional gynecologic conditions (1–9). This paper is a report of 10 cases of functional meno-metrorrhagia, treated with synthetic androgen (testosterone propionate), in which the therapeutic results were evidence of the usefulness of the male hormone in functional bleeding.

The rationale of this form of therapy and its margins of safety have been discussed at length elsewhere (10–13). Several investigators (14–18) have shown the bisexual action of the androgens in the female rabbit and spayed rats, manifest by estrogenic and progestational activity of the endometrium. (This does not occur in monkeys or human subjects.) Salmon (19) has shown that not only do androgens exercise a direct stimulating effect on the Mullerian tract of rats but they also produce follicle growth and corpora lutea in the ovaries of immature rats. This gonadotropic effect is mediated through the hypophysis (20).

The biological properties of the male hormone in women have been studied by many investigators. It has been shown that testosterone propionate inhibits the gonadotropic hyperactivity of the hypophysis of a castrate woman (3), suppresses menstruation (4), produces atrophy of the endometrium (21), deficiency changes in the vaginal smear (4) with disappearance of the glycogen (22), and inhibits peristalsis of the fallopian tubes (23).

Dosage. During this entire investigation an effort was made to achieve therapeutic results with as small a dose as possible. Some investigators used as much as 1000 mg. per month, and others reported results with as little as 30 to 75 mg. per month. We tried to strike a balance and used dosages varying from 45 mg. to 325 mg. per month. These dosages were administered in 10, 25 and 50 mg. injections of testosterone propionate (intramuscularly and subcutaneously) in sesame oil.

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CASE REPORTS

Case 1. H.B. age 22, complained of meno-metrorrhagia for a period of 18 months, following a spontaneous abortion. The first month we observed her she bled every day, using 6 to 8 pads daily. Pelvic examination revealed lacerated cervix and second degree retroversion of the uterus. Preliminary endometrial biopsy, during a bleeding phase showed an early proliferative stage. She was given 75 mg. of testosterone propionate in the next week, after which she noticed a definite diminution in the profuseness of the flow. The next month (now only bleeding very slightly) she received 265 mg. of testosterone propionate, and bleeding ceased at the end of the third week. Endometrial biopsy on the 19th day of cycle again showed an early inactive type of estrogenic pattern. The vaginal smears during this course of treatment all showed good estrogenic effect. (The psychological effect upon this patient was extraordinary, her personality reflected a new interest in life.) The third month she received 300 mg. of testosterone propionate and had only 3 days of actual bleeding with a few days of spotting. Biopsy again showed an early inactive proliferative phase, and the vaginal smear mirrored an adequate ovarian function. The next month she received only 40 mg. and had spotting 3 times during the month. Endometrial biopsies during the month showed no evidence of progestational effect. For the first 5 days of the fifth month of observation, she had normal bleeding for 5 days followed by 3 days spotting—no treatment at this time.

This case presents a prolonged meno-metrorrhagia from an estrogenic endometrium. Moderate doses of testosterone propionate, between 250 mg. and 300 mg. monthly, controlled the bleeding and showed regressive changes in the endometrium. She developed very slight hoarseness (which she thought was a cold) that disappeared when placed on smaller doses.

Case 2. M.B. age 26, colored, gravid 1, para 0 had had profuse meno-metrorrhagia for 8 months, requiring 10 pads daily, and had been confined to bed for at least 10 days to 2 weeks of the month. She received 170 mg. of testosterone propionate in the course of 1 week, immediately after this bleeding episode. After receiving 150 mg. she stopped bleeding, 20 mg. more was given and biopsy

showed a proliferative endometrium. She had no further abnormal bleeding and was completely relieved of any dysmenorrhea. She had 8 subsequent normal menstrual periods without further treatment. This patient was placed on methyl testosterone (oral androgen) as a maintenance therapy. (In the near future we hope to publish our observations of use of methyl testosterone.)

Case 3. K.B. age 26, had had meno-menorrhagia for the past 6 months, with dysmenorrhea requiring absence from work at least 3 days a month. Endometrial biopsy showed that she was bleeding from an estrogenic type of endometrium, with some beginning hyperplasia. The 1st month she bled profusely for 18 days, from an estrogenic endometrium. She received 110 mg. of testosterone propionate during the rest of the month. The 2nd month, spotting occurred the first 4 days and she was given 100 mg. testosterone propionate up to the 16th day. The flow was slight for 6 days, and heavy for only 2 days; there was no dysmenorrhea. This bleeding was also from an estrogenic type of endometrium. The remainder of the month she was given an additional 170 mg. The 3rd month, there was very slight bleeding from the 10th to the 16th day. There was no dysmenorrhea or ill feeling. She was given 260 mg. during the entire month, with no evidence of any disturbance in secondary sex characteristics. Spotting occurred the last 3 days of the month. Bleeding was again from an early proliferative endometrium. The 4th month, she received a total of 40 mg. during the entire month. Biopsy on the 7th day showed a beginning secretory effect, and she commenced to bleed on the 17th day, and had a normal period for 6 days, with slight cramps for one day. A total of 75 mg. was given during the 5th month and was followed by a normal menstrual period on 18th day of the month. Her general condition was very good. She gained weight, and is very happy.

This patient bled from an estrogenic endometrium controlled by moderate doses of testosterone propionate, and normal menses secondary to a progestational endometrium followed. Normal periods were maintained with 40 mg. to 75 mg. per month after bleeding was controlled.

Case 4. D.G., age 36, gravid 2, para 2, colored, had had menometrorrhagia for 6 months, with pain in lower abdomen and epigastrium. She had received anti-luetic treatment 5 years previously. Pelvic examination revealed a normal cervix, fundus anterior and slightly enlarged. A small non-tender nodule was found in the left fornix; the right fornix was tender and indurated. Insertion of a sound into the cervix was difficult because of a small cervical sub-mucuous fibroid about the size of a walnut. During the first month of treatment, she received 105 mg. of testosterone propionate prior to her menstrual period. The treatment seemed to have immediate effect in this case, and her menses were definitely less profuse, lasted only 6 days and were entirely free from any pain. Following her period she received 100 mg. during the rest of the month, and 40 mg. prior to the period the following month (total of 140 mg. from end of last menses to onset of present period). The ensuing menses lasted only 4 days, and were normal in character. We have followed her for 6 consecutive periods, which have all been normal, without any therapy.

Endometrial biopsies prior to treatment showed a swiss-cheese hyperplasia. The biopsy taken before the third menses while under our supervision, showed a normal progestational endometrium. Vaginal smears at all times showed a good estrogen effect.

Case 5. J.B. age 36, gravid 4, para 4, had had menometrorrhagia for 2 years. She had typhoid fever at 4, and pneumonia at 20 years of age. Operations she had had were a herniorrhaphy, cholecystectomy, and two vaginal plastics in the past ten years. Pelvic examination revealed the cervix soft and lacerated, fundus small and anterior, fornices negative.

This patient presented the most profuse and consistent type of bleeding we had seen. Her menses occupied 20 to 25 days of the month, some days requiring bed rest to alleviate the flow which was accompanied by hot flushes.

The first month under our care she received 150 mg. of testosterone propionate and very little effect was seen. The third day of the second month the endometrium showed a secretory effect. She received 100 mg. in the ensuing 8 days, and on the 9th day she commenced to flow moderately. This period lasted the entire month, with spotting the last 4 days. The first day of the month that followed she began to bleed moderately again, and this lasted until the 14th day. Biopsy at this time showed an early proliferative endometrium. She received 150 mg. prior to this biopsy and 175 mg. afterward, she did not bleed until the last 3 days of the month. The first day of the next month the bleeding again was moderate and lasted for 10 days. During this bleeding phase she received 75 mg. of testosterone propionate. One week later the endometrium showed an atrophic phase following dilatation and curettage. The patient desired removal of her uterus and a supravaginal hysterectomy was performed. Both ovaries appeared normal. The uterus was small and smooth. The pathological sections showed diffuse adenomyosis.

Although not more than 325 mg. of testosterone propionate was given in the first month to this patient, we did not notice any appreciable effect on the bleeding. After 150 mg. of testosterone propionate, given 2 weeks prior to endometrial biopsy, we found a secretory phase, which bled for 20 days. The following month, after 250 mg., the biopsy was of an early estrogenic type, and bleeding was diminished for 10 days. The 3rd month, after 250 mg. of male hormone, the biopsy showed an atrophic endometrium, and we observed the progress of the patient without any further androgen administration. Ten days later she commenced to bleed profusely again, this time for 3 weeks. At the end of this period she requested hysterectomy.

It is questionable whether the diffuse adenomyosis was the major contributing factor toward this bleeding; and would larger doses of male hormone

control such a pathological state of the myometrium? Investigators have reported cases that have not responded to androgen treatment, and it is a question whether these cases would fall into the category of adenomyosis. This is the type case we would classify under 'functional bleeding.'

Case 6. L.N. age 41, gravid 3, para 2, had had metrorrhagia for 3 years. Pelvic examination revealed a moderately soft cervix with horizontal laceration, fundus normal, some tenderness in left fornix, no masses. Endometrial biopsy showed a swiss-cheese hyperplasia; vaginal smear showed good estrogen effect. She received 85 mg. testosterone propionate prior to her period and for the first time in 3 years she did not have to go to bed because of profuse bleeding. The period lasted 5 days, with normal bleeding. From the onset of this period to the next which was 25 days, she received only 50 mg. testosterone propionate, and again the period was much less profuse than prior to treatment, but more than the previous period. Before the next period we will administer about 150–200 mg. and observe the effect.

Case 7. V.T. was 16 years of age, single; her menarche began at 13 years of age; menstrual periods were regular until 1 year ago, following an appendectomy. She had meno-metrorrhagia to the degree that her hemoglobin was 40%, and she was forced to miss a great part of her schooling. The rectal examination revealed a small uterus and cervix.

An endometrial biopsy on the 5th day of the month revealed a secretory phase; she menstruated 7 days later. This period lasted 10 days, with 4 days of profuse flow. Starting 5 days prior to her period and for the rest of the month she received a total of 175 mg. of testosterone propionate. The following month she was amenorrheic, but had cramps from the 10th to the 14th day, and again on the 21st day to the 24th day. During this month she developed slight facial acne. Unfortunately we could not obtain an endometrial biopsy this month. She received no injections at this time. The third month she began to menstruate on the 7th day and did not stop until the 31st of the month. She had 5 days of profuse flow, and the rest was spotting. In the last 2 weeks of this period she received 140 mg. of testosterone propionate. The following month she did not bleed until the 17th day, and this was from an estrogenic type of endometrium. The bleeding lasted 9 days, but was very slight. During this last month she received 60 mg. of testosterone propionate in all. The following month she had a period exactly 30 days from the onset of her last period, and this was bleeding from a progestational endometrium. During this month she received only 20 mg. of testosterone propionate.

Case 8. E.K. age 43, had had menorrhagia for 1 year. After a period of 10 days of very profuse bleeding a total of 175 mg. of testosterone propionate was given during the ensuing month, and she consequently had amenorrhea the following month. The endometrium during this month showed an estrogenic type, with tendency towards atrophy. After this amenorrheic month she received only 40 mg. of testosterone propionate and she had a bleeding cycle secondary to a progestational endometrium, with 10 days of spotting after 4 active bleeding days. During this spotting phase she was given 75 mg. of testosterone propionate and 125 mg. before the next period, which came on secondary to a secretory endometrium. The bleeding during this period was very scant (spotting) for 10 days. The next month she was amenorrheic after receiving 175 mg. of testosterone propionate. She did not receive any further treatment, and the next month she did not menstruate. The next month she resumed normal menstruation.

Case 9. R.S., age 34, had had menorrhagia for 9 months. Preliminary biopsy showed a hyperplastic endometrium. The first month she was given 50 mg. of testosterone propionate which lessened the profuseness of the flow (the following month) and the length of the bleeding days. Although she bled only 2 days less than the previous period, she felt "that the bleeding was under control." The next month she received 150 mg. of male hormone which likewise lessened the bleeding time to 9 days, and she had only 2 days of profuse flow. The premenstrual period showed an estrogenic type of endometrium. The third month she was given 257 mg. of testosterone propionate which definitely controlled the subsequent menstrual period. She flowed 6 days without any tendency towards profuseness. The following month she was not given any therapy. The premenstrual biopsy showed an advanced proliferative phase with some tendency towards hyperplasia. The menstruation was very profuse for 3 days and lasted 12 days. The next menstrual period was preceded with 150 mg. of male hormone, and the menses lasted 7 days with only 1 day of active bleeding. For the next 4 months she received 180 mg. testosterone propionate monthly, and her periods have been of normal quantity and lasting from 4 to 7 days.

Case 10 S.D., age 41, complained of prolonged periods, but not profuse, for 7 months. Preliminary biopsy showed a hyperplastic endometrium. She was given 125 mg. of testosterone propionate the first month, and the subsequent period was 2 days less. The second month she received 125 mg. of testosterone propionate and the following period was 2 days less but lasted 5 days. The third month she received no therapy and the period lasted 6 days. The next 4 months she had periods from 4 to 7 days, and on the eighth month she again had a 13-day menstrual period. The next 2 months she received 200 mg., and 125 mg. respectively, and had 5-day periods.

DISCUSSION

Ten cases of functional bleeding were studied over a period of one year. The age group was from 16 to 43; average age, 29. The 16-year-old girl was single, the others married. Six of the patients have one or more children, three never conceived. One had a small cervical fibroid, and one adenomyosis (post-operative). Six of the cases were classified as meno-metrorrhagia and four as menorrhagia.

One case of meno-metrorrhagia responded to one course of treatment, 170 mg. of testosterone propionate in one month, and had normal periods for 8 consecutive months. The case with the cervical fibroid received two courses of treatment (2 months),

total of 245 mg. and had 6 subsequent normal periods. Both cases required renewed treatment after 8 and 6 months respectively. Seven cases were controlled after 5 months of treatment; doses ranging from 50 mg. to 300 mg. per month. The one case of adenomyosis was not controlled, and came to operation, where we made the diagnosis only after examining the sections of myometrium. There was one case of slight acne and hoarseness, which cleared-up after treatment was stopped.

After observing these cases for one year, it was evident that testosterone propionate was of real value in the control of abnormal uterine bleeding. However, in order to achive this proper control moderate size doses had to be used; we could not get results with small doses. Although we had only a small series of cases, we must conclude that with moderate size doses (between 200 mg. and 300 mg. male hormone) the course of injections must be repeated anywhere from 4 to 8 months after normal periods are instituted. This mode of treatment is essential and has a definite place in gynecology, particularly where the young woman is concerned. It is this patient who is eager to preserve her reproductive ability, and likewise to be relieved of excessive bleeding who demands this type of treatment. There need be no fear of injury to the reproductive system. Huffman has shown that in rats, after large doses of testosterone, normal healthy litters were delivered; and the offspring in turn also showed perfectly normal evidence of procreation. We have had the opportunity to examine sections of ovaries of patients who had received large doses of male hormone, and found normally developing follicles and corpus luteum formation.

Huffman (30) recently described a large series of bleeding cases which were controlled by administration of 25 mg. of male hormone every other day, to a total of 250 mg. to 400 mg. In these patients the bleeding was completely stopped. To those cases of prolonged bleeding he gave 10 mg. twice weekly; this shortened or decreased the period. He found that the treatment must be repeated every 4 to 6 months.

In evaluating the study of the endometrium in these cases, it was found that bleeding can occur from any pattern, be it atrophic, proliferative, hyperplastic or progestational. The excessive bleeding phenomenon is not dependent upon the endometrial picture. A recent investigator (29) stated "uterine bleeding may proceed from every known type of endometrium; that the only common denominator is the recurrent vascular phenomena in the spiral arterioles; and that menstruation is fundamentally a vascular phenomenon." He concludes that the androgens inhibit the rhythmic intermittent contractibility of the myometrium, thus lessing the volume flow of blood to the uterus.

In all our cases, the first effect of androgen therapy was seen in delayed advancement of the normal physiologic endometrial cycle, along with a slight diminution in the character of the profuse flow. However, the small doses of testosterone propionate did not offer a reliable control of bleeding. The arrest of endometrial development with small doses of androgen would seem to be a local effect, with very little manifestation of lowered ovarian function. It was only with larger doses that definite regression of the endometrium pattern was seen, and here we assume that the ovarian function or pituitary—instead of, ovarian relationship was lowered. We have observed control of bleeding with regression of a hyperplastic endometrium to an early inactive proliferative phase with 265 mg. of testosterone propionate given during the month; and the endometrium build up to an advanced proliferative phase with early development of cystic hyperplasia, along with an increase in the menstrual flow.

It was necessary to maintain an 'estrogen:androgen balance' after the initial bleeding was controlled by administration of at least 25 mg. of testosterone propionate twice weekly. That such an estrogen:androgen balance may exist was shown by Hamblen, Pattee and Cuyler (28). Their work supports the belief that an estrogen:androgen balance exists which is altered by changes in the concentration of the component elements; but these studies do not warrant the assumption that estrogen therapy can negate the virilizing effects of excessive androgenic secretion associated with hyperplasia or neoplasm or the adrenal cortex.

Testosterone propionate will inhibit the gonadotropic activity of the hypophysis (when given in large doses during the first two weeks of the cycle) and delay menstruation for the ensuing month. The following month, however, a normal ovulatory menstruation may take place. When moderate doses up to 300 mg. per month are given, the function of the ovaries is only partially inhibited and bleeding will occur, but the profuse menorrhagia will be controlled. To maintain this control testosterone propionate in moderate doses must be given fairly consistently in most cases.

In this study to control functional bleeding with the smallest doses possible, we were impressed by the fact that some women (two in our series) will respond to initial small doses of male hormone, while others require monthly (small to moderate) doses in order to maintain normal menses.

We followed the effect on the vaginal smear in these cases and found not one that we could call an advanced estrogen deficiency as classified by Geist and Salmon (25). We wish to emphasize that the deficient vaginal smear as well as the masculinizing ef-

fects will not be seen if the dosage of androgen is kept around the 300 mg. level. Should a deficient smear be seen it should be used as a warning sign to stop treatment.

It has been shown that the normal menstruating woman excretes an averages of 26 I.U. of androgen daily, whereas before puberty the androgen excretion is from 1.8 to 2 I.U. per liter (26).

SUMMARY

The effect of testosterone propionate was studied in 10 cases of abnormal uterine bleeding over a period of one year. Endometrial biopsies and vaginal smears were taken before, during and after administration of the male hormone.

Testosterone propionate in moderate doses, ranging from 50 to 150 mg. monthly will arrest the normal cyclical development of the endometrium, and definitely lessen the profuseness of the uterine bleeding, but it will not stop the bleeding in most cases.

Testosterone propionate up to 325 mg. per month will stop bleeding in most cases; produce subsequent amenorrhea the following month, and cause inactivity to atrophy of the endometrium. The vaginal smear with this size dose shows little signs of regression. Masculinizing effects are rare.

One uncontrollable case was found to have adenomyosis uteri.

Abnormal bleeding may occur from any type of endometrium.

The course of injections with testosterone propionate must be repeated every 4 to 8 months.

The testosterone propionate used in this investigation, was supplied by the Schering Corporation, Bloomfield, N. J., through the courtesy of Dr. Max Gilbert, and by Ciba Pharmaceutical Products Inc., Summit, N. J., through the courtesy of Mr. Robert C. Mautner.

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DYSMENORRHEA

ANHYDRO-HYDROXY-PROGESTERONE IN DYSMENORRHEA

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DYSMENORRHEA is a gynecological condition apt to respond with most startling and brilliant results to therapy and also is liable to give most disappointing responses. As Plass (1) states, "dysmenorrhea is a purely subjective complaint and therefore most difficult to evaluate." The psychogenic status of the patient deserves the deepest consideration. Mathieu (2) notes that the pain of dysmenorrhea has to do with the uterus . . . and it is quite certain that the pain is due to contraction of an irritable uterus provoked by the presence of blood in its cavity. The 'psychogenic woman' feels these physiological contractions as severe spasmodic pain, whereas the average woman notes the same degree of contraction as mild distress or not at all. Certain authors have overemphasized the psychic factors in the diagnosis and treatment just as others have actually and decidedly neglected this important phase of the subject.

The actual mechanism of the pain of dysmenorrhea has been discussed widely by numerous observers and there is certainly no universal agreement. Those cases of dysmenorrhea associated with organic pathology such as endometriosis, chronic pelvic inflammation, stenosis and tumors are easily understood. Experimental evidence indicates that estrogenic hormones stimulate contractions of the uterus (3, 4). Thus, should there be an excess of estrogenic hormones, the contractions of the uterus might become abnormally severe and produce painful sensations. Also, the uterus may be underdeveloped and thus respond abnormally to stimulation of an otherwise normal estrogenic hormone level(1). Experimental work also indicates that the corpus luteum hormone inhibits or quiets contractions of uterine muscle (5). Macht (6) and Campbell and Hisaw (7) base the rationale of therapy of dysmenorrhea with corpus luteum on this antagonistic action of the corpus luteum hormone to the action of estrogenic hormone.

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There is not a universal acceptance of this theory of the etiology of dysmenorrhea. Moir (8), Lackner, Krohn and Soskin (9) and Wilson and Kurzrok (10) offer evidence to indicate that the amplitude of uterine contractions is greater during the luteal phase than in the follicular phase of the menstrual cycle. As Miller (11) states, "if these findings be accepted unqualifiedly, it can scarcely be assumed that progesterone is an inhibitor of uterine contractions in the human being."

Without attempting to delve further into the theories of cause of dysmenorrhea, it is plausible to assume that certain types of dysmenorrhea are hormonal in character. It is this group which has shown satisfactory response to thyroid, to insulin (12) and to progesterone.

The use of progesterone in dysmenorrhea has progressed for several years and an increasing literature is accumulating. Varying dosage of from 0.08 to 5 or more units have been administered (7, 13–15). The general consensus of opinion is that this form of therapy gives good results. There is complete relief of dysmenorrhea in half or more of all patients treated. There is no assurance to the patient as to the permanence of relief. There are no notable changes in general physical or laboratory findings.

Various hormones have been isolated in pure forms and have then been synthesized. Progesterone was thus developed. Progesterone was isolated in 1934 almost simultaneously by three groups of workers (16, 17, 18). The hormone is found almost exclusively in the corpus luteum, but some is also found in the placenta and in the adrenal glands of certain species. It is excreted in the urine as pregnandiol. Progesterone is effective only when given parenterally. It is usually dissolved in an oil.

Further research resulted in an orally effective sterol with progestin properties. This preparation, anhydro-hydroxy-progesterone is closely related to the female sex hormone, progesterone, and by another name, ethinyl testosterone, can be noted to be similar

ORAL USE OF ANHYDRO-HYDROXY-PROGESTERONE IN DYSMENORRHEA

Case No.	Age	Menses, interval, duration	Pain			Genitalia	B.M.R.	Anhydro-hydroxy-progesterone			Results
			Before flow	With onset of flow	During flow			Daily dosage	Number days	Total dosage	
								mg		mg.	
1	23	28/5	0	0	+	Normal	−30	40	3	120	Excellent
2	31	28/7	+	+	+	Normal	− 1	20	7	140	No response
3	25	32/3	+	0	+	Uterus small	−23	30	8	240	Excellent
								30	8	240	Excellent
4	26	24–32/3	0	+	+	Normal		40	5	200	Excellent
5	23	28/5	0	0	+	Normal		40	4	160	Good
6	28	22–40/6	+	+	0	Uterus small		40	7	280	Excellent
7	33	28/4	+	+	+	Uterus small		60	5	300	Excellent
8	23	30–31/3	+	+	0	Uterus forward with pessary	− 3 −14	10	21	210	Excellent
9	32	28–34/6	0	+	0	Normal	−18	2(H)	1		Excellent
10	18		0	+	0	Mild genital hypoplasia	−28	40	6	240	Excellent
11	35	28–35/3	+	0	0	Normal	+ 7	30	12	360	No response
12	30	28–30/5–7	+	0	0	Marked hypoplasia with retrodispl.		40	4	160	Good
								40	6	240	Excellent
13	25	28–38/6	0	+	0	Normal	−11	100	1	100	Good
								40	6½	260	Excellent
								40	7	280	No response
14	22	23–24/7–8	+	+	+	Marked hypoplasia with retrodispl.	− 8	5	10	50	No response
								60	3	180	Worse
								50	5	250	No response
15	32	32–33/5–9	+	+	+	Uterus very small	− 7	40	6	240	No response
16	24	28–29/5	+	+	0	Normal	−11	5	8	40	Poor
								60	6	360	Excellent
17	18	26–28/3–4	+	+	+	Retrodisplacement	−15	30	6	180	Good
								60	3	180	Poor
								60	6	360	Excellent
18	23	26–42/6	0	+	0	Normal		40	4	160	Poor
								30	11	330	Good
19	20	28/5	0	+	+	Normal		40	4½	170	No response
20	23	28/4	+	+	0	Normal	−13	60	5	300	Excellent
21	26	26/5	+	+	+	Mild hypoplasia with retrodispl.	−24	60	5	300	No response
								60	5	300	Excellent
22	31	25/7	0	+	0	Small myoma		60	5	300	Worse
23	23	28–50/4	+	+	0	Normal		30	14	420	Excellent
								40	12	480	Excellent
25	21	28/4	+	+	0	Normal		60	5	300	Excellent
								60	5	300	Excellent
26	21	28–31/6–7	0	0	+	Normal		40	5	200	Excellent
27	33	28/5	+	+	0	Normal		60	6	360	Worse
28	29	60–120/6	+	+	+	Normal	−27	60	6	360	No response
29	25	28/5	+	+	+	Normal		60	6	360	Worse

to the male sex hormone. Anhydro-hydroxy-progesterone has been evaluated in the treatment of functional menorrhagia and metrorrhagia (19).

The present report concerns itself with 28 cases of dysmenorrhea treated from one to three months with anhydro-hydroxy-progesterone in various dosages.

The range of age of onset of menses was from 11 to 15 years. In none of these patients was there any greatly significant deviation from normal habitus, hair distribution or appearance of the external genitalia. In several patients, the uterus was somewhat smaller than normal, and in 2 cases there was an extremely marked under-development of the internal genital structures. One patient had a small myoma of the uterus.

It was realized that many of these patients probably needed and might have responded equally well to thyroid. Five of these patients have been on thyroid therapy at various times, independent of this study. Two of the five obtained complete relief of their dysmenorrhea with thryoid. Both of them responded equally well to anhydro-hydroxy-progesterone.

Six of the patients in this study had been pregnant. Five of them had dysmenorrhea before their pregnancy and it was present in equal severity after the resumption of menstruation following pregnancy. One patient acquired the dysmenorrhea after pregnancy when it had not been present prior to pregnancy.

RESULTS

A series of 28 patients were observed through 40 menstrual cycles while being treated with anhydro-

hydroxy-progesterone orally. Twenty of the 28 patients were benefited, an incidence of 71%. When studied from the point of view of menstrual cycles, either good or excellent relief was obtained in 25 of the 40 cycles, an incidence of 62%.

The patients in this series were given no other medications, placebo or active, during the course of observation.

Care was taken not to emphasize the medication in any way which might result in a favorable psychic response.

The age incidence was from 18 to 32 years.

The interval and duration of menses was essentially normal. Patients *23* and *28* gave a history of prolonged periods of amenorrhea. Patients 6 and *14* presented menses of shortened cycles.

General physical examination, hair distribution and appearance of the external genitalia was essentially normal in all cases. In several cases the uterus was smaller than normal. Patients *12* and *14* exhibited a marked hypoplasia of the internal genitalia with retrodisplacement. Retrodisplacement of the uterus was noted in several cases. One patient presented a small myoma of the uterus.

The basal metabolic rate was determined in 16 cases and was uniformly low. Even though many of these patients might have been treated with thyroid extract, none were so treated during this series.

Pregnancy did not relieve the distress of any of the 5 patients who gave such history of dysmenorrhea prior to the gestation.

Anhydro-hydroxy-progesterone was administered orally in dosage from 5 to 100 mg. daily and for from 1 to 14 days. The total dosage varied from 40 to 480 mg. per cycle.

The optimum dosage seems to be about 60 mg. daily for 5 to 6 days immediately premenstrually and with the medication being administered right up to the onset of flow.

In no instance was permanent relief observed. The usual situation was for the patients to request the medication during subsequent cycles. No untoward effects were noted.

SUMMARY

Some of the current views regarding the etiology and therapy of dysmenorrhea are discussed briefly. Anhydro-hydroxy-progesterone was administered orally to a series of 28 patients through 40 menstrual cycles. No other medications, placebo or therapeutic were prescribed during treatment with anhydro-hydroxy-progesterone.

Seventy-one per cent of the patients were benefited by the medication. Sixty-two per cent of the menstrual cycles were free of pain. The dose of anhydro-hydroxy-progesterone for effective results in dysmenorrhea is approximately 60 mg. daily for the five days immediately premenstrual. Subjective relief occurred essentially only with treated cycles. No curative effects were observed. No untoward effects were noted.

The anhydro-hydroxy-progesterone used in this study was supplied as Pranone through the courtesy of Dr. Max Gilbert of the Schering Corporation, Bloomfield, N. J.

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MALE HORMONE SUBSTANCE:[1] A PRIME FACTOR IN ACNE

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ACNE

ADMINISTRATION of male hormone substance has been observed to result in acneform eruptions in an eunuchoid man (1). In this instance the formation of acne was clearly and unmistakably associated with the androgenic therapy, a fact confirmed in another eunuchoid individual (2). The present report is an analysis in men, women and children of the relationship of androgens to experimentally induced and naturally occurring acne. Before presentation of these observations brief statement and evaluation are given of the nature of sebaceous secretions and of certain basic data about acne such as incidence and conceptions of etiology, pathogenesis and the influence of endocrine and other factors.

I. Incidence of Acne

Acne accounts for about 7.5% of all cases seen in the practice of dermatology in America (3), occurring most commonly during adolescence and shortly thereafter (4, 5, 6, 7). Obviously this percentage does not include individuals who apply only to the general practitioner or do not consult a physician.

The prevalence of acneform eruptions with concomitant disfiguration and psychologic trauma has been long recognized. Cassius (100 A.D.) inquired why acne should occur in the prime of youth and strength and came to the conclusion that "the noblest and best elaborated nutritive fluids are determined to the regions affected, and there stagnate and accumulate" (8).

A comprehensive study has been made by Bloch (9) of 2,136 girls between 6 and 18 years of age and of 2,055 boys between 6 and 19 years of age. He found that of the 17-year-old girls only 5.3 % and of the 18-year-old boys only 0.6 % have no comedones (fig. 1). Bloch believes that acne, especially the comedo, accompanies other physiological events in puberty so commonly as to demand the interpretation that it represents a physiological rather than a pathological phenomenon, and, therefore, is a phase of normal puberty. This is the opinion held by Darier (10) and Michael (11), but is not universally accepted. A study of the incidence of acne in 872 males and 1,180

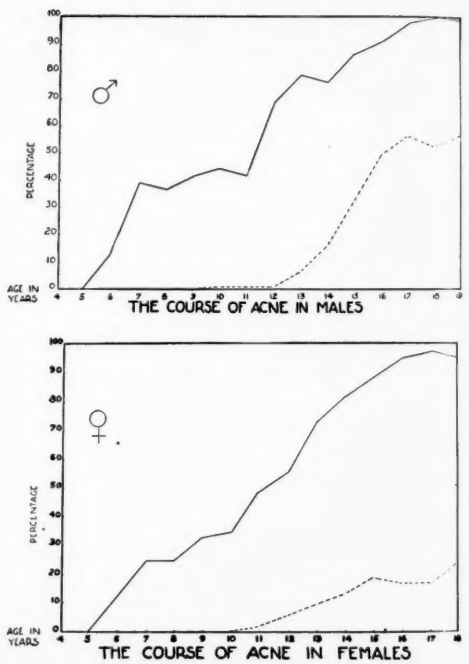

Fig. 1. (Adapted from data of Bloch (9).) The incidence of acne reaches a peak during adolescence, at least comedones developing in almost every boy and girl 17 or 18 years of age. Severe acne is found predominantly among boys. Solid line, over 50 comedones, papules or pustules at the time of observation. Broken line, comedones, papule or pustule.

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females between 5 and 22 years of age in the Chicago area (12), using the same manner of tabulation as Bloch, confirmed the high incidence of acne at puberty. In contrast to the findings in Switzerland there was a greater incidence of acne in the Chicago area and an earlier appearance of severe stages in girls than in boys.

II. Sebaceous Secretions and the Pathogenesis of Acne

A. The sebaceous glands. Sebaceous glands are located in the dermis over most of the body except on the palm of the hand and sole of the foot. Usually the glands open into the neck of a hair follicle, the close association of these two structures being recognized by the joint name of pilosebaceous system. The largest glands, those on the nose, have only minute hairs, however; and in limited regions the sebaceous glands are unaccompanied by hairs, as on the lips, corners of the mouth, internal surface of the prepuce, glans penis, labia minora, mammary papillae and the tarsal glands of the eyelids.

Most sebaceous glands consist of a group of secretory alveoli which open by a common duct into the cavity of the hair follicle. The excretory duct is lined with stratified squamous epithelium, whose cells merge with those of the basal layer of the epidermis and with the epithelium of the external root sheath of the hair.

An alveolus of a sebaceous gland is filled with cells, those in the center being larger in size than the ones at the periphery. The cytoplasm of the central cells consists almost entirely of fat droplets; the nuclei are small and the cells are undergoing disintegration. Sebaceous secretions are usually considered to be formed by the breakdown of the entire cell, a process known as holocrine; thereby not only fatty material but also cell debris is contributed. There are claims, however, that sebum represents secretion through the cell membrane rather than fatty degeneration of the cell (13). Desquamated cells from the epithelial lining of the ducts are added to the sebaceous secretions.

B. Sebum. Sebum, the secretion of sebaceous glands, is a semi-fluid mixture which upon expression from the follicles covers the surface of the skin with an oily layer. When retained in the follicle it is more viscous and of the consistency of soft cheese. Sebum contains a trace of glycerides and large amounts of esters of fatty acids with the higher alcohols, such as cholesterol (14).

Starling (14) states that the extrusion of sebum is accomplished by contraction of the arrectores pilorum and that such expulsion has been shown experimentally to accompany faradic stimulation or the application of a cold object. Even though such action occurs, there is no proof that this mechanism is responsible for the outflow of all sebum and there is reason to doubt the necessity for dependence of normal expulsion upon contractions of cutaneous muscles despite the comment (15) that acne does not occur in the scalp, a region with well-developed integumentary musculature. The forehead has the largest quantity of sebaceous secretions per unit area of any integumentary surface subjected to measurement (16), yet is practically devoid of arrectores pilorum. Regulation of the outflow of sebum depends in all likelihood upon the, thickness and viscosity of the layer of oil upon the skin and upon the size of the secreting sebaceous elements (16).

C. Comedo formation. The early manifestation of the acneform eruption, that is, acne in the broadest sense (9), is the comedo or blackhead. This is a mass of secreted material plus debris which is retained within the follicle. The commonly-held concept is that hyperplasia of epithelial cells at the mouth of the follicle is responsible for retention of the secretions (17, 18, 19). Such hyperplasia is evident at puberty and upon irritation of the skin surface as by paraffin, but mere presence affords no proof of a primary or even major function in acnegenesis and the usual blind acceptance of this dogma must be criticized until conclusive evidence is gained.

There is also increased secretion of sebum. Retention of sebum may be due to closure of the follicular outlet but until excluded by incisive studies other possibilities must be recognized such as change in the consistency and nature of sebum, growth of the gland and components of the hair sac and even immunologic responses and phenomena occurring in the surrounding integument.

D. Transformation of comedo to papule and pustule. Inflammatory and infectious processes may be superimposed upon the tissues surrounding the plug of sebaceous material in the follicle. Intermingled with sites which remain in the comedo stage are pilosebaceous systems which become the seat of inflammation and infection and are known as papules and pustules. The degree of inflammation and infiltration varies with the constitution and status of the patient, the location and nature of the lesion and unknown factors.

III. Etiology of Acne

The lack of sound data regarding the etiology of acne is directly proportional to the number and variety of purported causes: infection; intestinal intoxication; derangement of carbohydrate, sugar, cholesterol and fat metabolism; gastric acidity; allergic and psychoneurogenic phenomena; toxic excretions of the sebaceous follicles and lastly, each of many endocrine secretions, especially those of the thyroid gland. Many of these claims do not seem to be warranted and in some instances have been disproven.

To facilitate discussion acnegenesis is considered from two viewpoints, (*a*) sensitivity of the pilosebaceous apparatus and other tissues and (*b*) agents that stimulate these structures. Both agents and the sensitivity of the integumental (and perhaps additional) structures are probably involved.

A. Sensitivity of pilosebaceous apparatus. In patients exhibiting acne Sulzberger, Rostenberg and Sher (20) have made initial attempts to test the sensitivity of the follicular epithelium to various irritants without obtaining conclusive results; the authors did show, however, that patients with acne responded uniformly with exanthema when potassium iodide was ingested, a reaction seldom found in persons without acne. Since acne was already present, however, the stimulating agent cannot be stated

to have produced acne. These results are merely an expression of the reactivity of the integument in the patient who already has acne, and as such may be related to the existence of acne or to other factors besides those responsible for the induction of acne.

1. *Congenital and apparently familial factors.* Congenital predisposition in the capacity for acquisition of acne is apparently indisputable (21, 22, 23), notwithstanding the occurrence of acne in only one of a pair of identical twins (24). Siemens (21, 22) studied 28 pairs of identical twins and 6 pairs of fraternal twins, finding that in identical twins the distribution and character of juvenile acne can be practically identical, whereas it is decidedly different in twins from separate ova. He found also that there is an hereditary predisposition to acne like that to freckling.

2. *General bodily state.* The general physical and mental condition is not without influence but there is no unanimity of opinion as to the manner in which this affects the capacity of the skin for acneform eruption.

The relationship of a diet high in carbohydrates to pyogenic infections is often the basis for the advocation of low carbohydrate diets for patients with pustules (25). Interpretation by analogy to gangrene in diabetes has been suggested, but obviously there is no strict similarity to the localized folliculitis of acne.

Usher and Rabinowitch (26) found that in persons with low sugar tolerance, the administration of dextrose resulted in a manifold increase in the amount of sweating and in an elevation of 100% or more in the sugar content of this secretion. It was pointed out that the high sugar content of sweat affords good culture media for bacteria. There appears to be no necessary correlation between folliculitis of sebaceous structures and activity of sudoriparous glands; indeed, the vasomotor disturbances and profuse sweating that ensue upon castration of some men are not conducive to acnegenesis, whereas administration of androgens to these castrates may suppress the tendency to pronounced perspiration but result in the appearance of acne.

Studies of glucose tolerance have revealed no definite difference between individuals with and without acne (27, 28). The level of blood sugar has been said to be high in patients with acne (29, 30), but many workers have denied or have not been able to confirm the existence of such a relationship (31, 32, 33, 34). Further, in attempts to correlate acne and the carbohydrates in the diet, normal periodic changes in the blood sugar content (35) have not received consideration. Although it remains suggestive that administration of added amounts of carbohydrates is said to augment markedly sebaceous secretion (36, 37, 38), other technics than quantitative measurement of blood sugar and sugar tolerance may be required to probe this matter satisfactorily.

Reactions apparently related to the ingestion of certain foods have been reported (39, 40, 41). No one or even several foodstuffs seem to offer a common denominator in the induction of acne, although exacerbations may be produced. Strickler and Adams (42) were unable to associate acne with the cholesterol content of the blood, and Knowles and Decker (43) found nothing pertinent in gastric analyses.

Constipation, colds and other infections were of the same approximate character and quantity in 2,974 women with acne and in 3,185 women without acne, as shown in a study of college students (44). Hinrichsen and Ivy (12) also found no correlation between acne and loci of infections in their extensive series of cases.

The factors in the general bodily state described above have not been shown to be the cause of acne, but the possibility of their influence upon the course of eruptions in the individual person is, of course, not excluded.

B. Agents acting upon the pilosebaceous apparatus. Secretion and outflow of sebaceous material may be influenced by secretagogues, skin irritants and infectious processes as well as by the status of the sebaceous glands and by physical properties of the oily layer already overlying the skin.

1. *Skin irritants.* These may act externally or internally. Acne is common among those who work with grease and oils, presumably due to clogging of the follicular outlet. The ingestion or injection of certain drugs may result in eruptions, according to some authors because of excretion by the follicles of these drugs or their end-products. Bromides and iodides are especially effective in this regard. Stein (19) and Kleeberg (45) outline the theory that acne vulgaris is an excretion response of the follicles to metabolic end-products of intestinal or gonadal origin, in the manner that halogens are claimed to be excreted by the sebaceous glands.

2. *Local infection.* The prevailing opinion of dermatologists appears to be that a number of factors may be concerned in acne vulgaris, and those who consider it a local infection (46) are apparently in the minority. There are substantial reasons for dispute over the selection of a single type of bacterium as a universally causative agent (46, 47, 48). *Corynebacterium acnes* was apparently obtained by Unna from comedones. Sabouraud (46) obtained pure cultures of a morphologically similar bacillus. Gilchrist (49) stated that *C. acnes* is pathogenic in mice and guinea pigs, but Südmersen and Thompson (50) found it pathogenic to mice only upon intraperitoneal injection. A common belief among dermatologists is that although *C. acnes* can be cultured from comedones, suppuration is ascribable to secondary infection with staphylococci (51, 52).

Ramel (53) and Kemeri (54) suggested that certain types of acne were of tuberculous origin. This does not afford a logical or demonstrable explanation of any large percentage of the cases of pubertal acne.

The present report would attempt to establish the primary importance of secretagogues like the androgens and of a secondary, dependent rôle of bacterial infection in the folliculitis, in as far as function of sebaceous glands may be a *sine qua non* for at least certain types of folliculitis. It is not implied that bacterial flora of the skin be regarded as saprophytic or without a major rôle in papule and pustule formation, but only that the stimulation of sebaceous secretions may be a necessary prelude in the ordinary patient to bacterial action in the acneform response. The presence of bacteria and on occasion even parasitic worms in the follicles is not to be denied, and loci of infection elsewhere in the body are not without effect on the condition of the body and skin. Especial

attention has been directed (17, 41) to the scalp as a focus of reinfection in acne.

3. *Physical properties of the oily layer over the skin.* Emanuel (16) has indicated that the expulsion of sebum from the follicle is controlled in part by the viscosity and extent of the oily layer of the skin. Since the type of fat ingested affects fat deposition, it may be that the type of ingested fat is not without influence upon the constituents of sebum.

4. *Secretagogues of sebaceous glands.* A relationship between the endocrine system and the skin exists in a wide variety of disorders such as of the thyroid as in myxedema, of the parathyroid as in osteitis fibrosa, of the gonads as in hypogonadism and castration, of the adrenal cortex as in adrenal virilism and as in cortical atrophy, and of the pituitary as in acromegaly.

In some instances the relationship between the endocrine system and the skin postulates a secretagogue of sebaceous glands. No endocrine substance has been demonstrated, however, to act as such a secretagogue. Hollander (55) speculated that acne might represent abnormal thyroid function, but McCarthy and Hunter (56) showed that secretions of the thyroid are not a major factor in aberrant function of sebaceous glands in acne.

IV. Criteria in Determination of the Nature of Hormone Incitants of Acne

Although the influence of endocrine factors is indicated by the onset and course of acne concomitant with the assumption of physiological activity on the part of the gonads, no proof is afforded thereby of processes or chemical substances involved. Innumerable postulations have been advanced; the pituitary, thyroid, testis, ovary, adrenal—or combinations of various glands—have been held to be responsible. Actually the designation of a gland as 'responsible' for acne is in itself not a matter of great moment. It is the secretions of the gland and their metabolism that are significant. One gland can produce more than one type of hormone; secretions of the ovary, for example, may be either androgenic or estrogenic. Similarly the hormones can be converted in the human body into entirely different substances, male hormone substances (androgens), for example, being converted into female hormone substances, the estrogens (57, 58, 59). Further, the absolute and relative quantities of the hormones significantly affect their action; for instance, estrogens and androgens may act antagonistically in certain respects (60). A clear demonstration of the factors inducing skin eruptions would be best afforded by administration of crystalline hormone rather than by interpretation of phenomena affected in an uncontrolled manner by a mixture in the bodily tissues and fluids of gonadal secretions that are unknown in quantity and in quality.

The second requirement for proper examination of the relationship of gonadal hormones to acneform eruptions is a satisfactory type of individual for the testing of the skin response. To provide a suitable test the patient should have low levels of the hormones in the bodily tissues and fluids; otherwise the administration of hormone affords a measurement of only relatively more hormone in an individual who already possesses a considerable amount of hormone substances. The criteria for suitable test subjects are most satisfactorily met in the following persons: children before puberty, and individuals who either have not matured sexually (eunuchoid) or have been castrated after reaching maturity (eunuch). All three types of males have been tested: prepubertal boys, eunuchoid and castrate men.

V. Objectives

A. Examination of the sexual status of the individual including measurement of urinary titers of androgenic, estrogenic and gonadotropic hormones in eunuchoid and castrate men (*a*) before, (*b*) during and (*c*) after administration of exogenous hormone; correlation between sexual status and the course of acneform eruptions.

B. Proof that crystalline sex hormone can produce acne in susceptible persons, male and female.

C. Observations of the acne induced upon administration of hormone; comparison with acne vulgaris.

D. Measurement of increase in sebaceous secretion induced by the hormone; relation to etiology of acne.

E. Relation of skin eruptions to other phenomena accompanying the presence of administered hormone.

F. Differential response of the pilosebaceous apparatus to skin irritants when the patient is, respectively, with and without hormone treatment.

G. Designation of the actual chemical substances involved in the production of acne.

H. Examination of clinical conditions accompanied by acne with regard to rôle played by male hormone and other substances.

SUBJECTS, MATERIALS AND METHODS

Thirty-one boys were examined for comedones and skin eruptions before, during and after the administration of the male hormone substance, testosterone propionate,[2] given as trial therapy in certain types of cryptorchidism. The ages of the boys ranged from 2 to 17 years (plus two cases, 20 and 23 years old, respectively); they received courses of from 5 to 10 mg. to androgen given intramuscularly 3 times a week for a period of 12 weeks. After an interval of about 4 weeks another period of treatment was employed in some instances for stimulating growth of genital structures preparatory to surgery. Injections of similar quantities of peanut oil containing no hormone were given to allow control observations of possible effects of the vehicle.

[2] Testosterone propionate, in the form of Perandren, and androsterone were furnished by Ciba Pharmaceutical Products, Inc., Summit, N. J.

TABLE 1. BOYS AND YOUNG MEN WHO RECEIVED INJECTIONS OF TESTOSTERONE PROPIONATE AS TRIAL THERAPY FOR CRYPTORCHIDISM

Case, age in yr.	Amount of testosterone propionate	Duration of treatment	Color			Type of response		Place of reaction
			Skin	Hair	Eyes	Comedo	Papule	
	mg.	*weeks*						
W.C., 10	425	18	Fair	Brown	Blue	+	o	Nose
W.W., 2	220	14		Colored		o	o	
F.B., 13	460	13	Olive	Dark	Brown	+	+	Nose
W.A., 8	530	17	Fair	Red	Blue	+	+	Nose
R.H., 11	450	17	Fair	Brown	Brown	+	o	Nose
A.P., 7	290	26	Fair	Dark	Brown	+	o	Nose
E.P., 4	350	22	Fair	Brown	Brown	+	o	Nose
W.F., 17	380	11	Fair	Brown	Blue	++	o	Nose, chin
T.D., 2	230	16	Fair	Brown	Brown	o	o	
W.M., 9	285	15	Fair	Lt. br.	Blue	++	o	Nose
G.H., 9	340	14	Fair	Blond	Brown	++	+	Nose, back, face
R.S., 10	250	13	Fair	Brown	Brown	+	o	Nose
R.V.B., 16	430	18	Olive	Dark	Brown	o	o	
S.S., 13	375	27	Fair	Dark	Brown	+	o	Nose
E.S., 5	85	7	Fair	Red	Blue	o	o	
C.S., 10	445	18	Fair	Brown	Brown	++	o	Nose
J.B., 20	390	11	Fair	Brown	Brown	o	o	
W.D., 23	1,810	38	Fair	Brown	Blue	+	++	Nose, back
E.M.K., 9	620	23	Fair	Red	Blue	++	o	Nose
R.B., 13	650	23	Fair	Brown	Blue	+	o	Nose
A.R., 3	470	18	Fair	Brown	Brown	o	o	
H.R., 14	335	13	Fair	Brown	Blue	o	o	
J.A., 10	1,015	35	Fair	Brown	Blue	++	o	Nose
K., 12	390	15	Fair	Light	Blue	o	o	
R.V.H., 13	925	31	Fair	Light	Blue	++	o	Nose
T.F., 11	855	29	Fair	Brown	Brown	+	o	Nose
J.L., 12	340	11	Fair	Brown	Brown	+	o	Nose
T.R., 12	605	24	Dark	Dark	Brown	+	o	Nose
G.S., 11	210	12	Fair	Light	Blue	+	o	Nose
J.G., 9	90	9	Fair	Brown	Brown	+	o	Nose
M.W., 8	130	12	Fair	Brown	Brown	o	o	

Eight eunuchoid and castrate men between the ages of 18 and 45 were also given mock treatment and at later periods treated with active male hormone substance. Three other eunuchoids and one castrate were examined but not treated. Description of these men is given in table 1 and elsewhere (1, 61, 62). Various doses of male hormone substances were employed from time to time. These included 20 mg. of testosterone propionate injected intramuscularly 3 times a week and later 7 times a week for periods of from 4 to over 70 weeks. In occasional instances methyl testosterone was given orally, or pellets of testosterone propionate were implanted subcutaneously. Alternation of periods with and without the use of medication has been continued for over 3 years in some individuals.

Two ovariectomized women were studied following intramuscular administration of 20 mg. of testosterone propionate 3 times weekly for from 3 to 7 weeks. Both were in their fourth decade and had undergone ovariectomy one and two years, respectively, prior to treatment.

Testosterone propionate was usually dissolved 20 mg. in a cc. of peanut oil. Intramuscular injections were made either in the upper arm or in the buttocks. The comparative effectiveness of testosterone given orally or by subcutaneous injections is described elsewhere (63).

Prior to treatment quantitative determinations were made of urinary estrogenic, androgenic and gonadotropic substances. All urine samples represented the complete output for 24 consecutive hours. Collections for 4 or more days were generally employed for each determination in an attempt to minimize daily variation. Toluene was used as a preservative and the extraction was not delayed. The method used for extraction of the androgens and estrogens was that of Gallagher et al. (64). Androgenic activity was determined by bioassay with the chick comb as described by Dorfman and Greulich (65). A minimum number of 15 and usually 20 chicks was used for each assay. The accuracy of the determinations is held to be $\pm 25\%$ and is probably greater. All values are expressed as international units (I.U.) per 24 hours. An international unit of androgenic activity is that evoked by 0.1 mg. of androsterone.

Assays of estrogenic activity were carried out with adult spayed female mice, 10 or more of which were used for each assay. Estrogenic values are expressed in terms of the international unit (I.U.) which is that evoked by 0.1γ of estrone. The method of extraction was that of Gallagher et al. (64). Gonado-

TABLE 2. ACNEFORM ERUPTIONS AND THE ANDROGENIC STATUS IN A SERIES OF EUNUCHOID AND CASTRATE MEN

Case number, age and status	Urinary excretion per 24 hours			Testosterone propionate		Type of acneform response			Site
	Andro-gens	Estro-gens	Gonado-tropins	Amount	Dura-tion	comedones	papules	pustules	
	I.U.	I.U.	M.U.						
1, 27 yr., hypogonadal with eunuchoid proportions and genitalia, ht. 175 cm., wt. 79.0 kg.	14.1	12	5			Before therapy never had acne			
	89.0	41	3.5	550 mg.	5 wk.	++	++	++	Face, neck, back, chest, shoulders
				None	6 wk.	Acne quickly faded and gradually disappeared			
				50 mg.	5 wk.	+++	++		Same as before
				320 mg.	8 wk.	Severity diminished with continued treatment			
				None	26 wk.	Acne disappeared			
2, 35 yr., unilateral cryptorchid until age of 35, when descended testis was operatively removed with resulting severe castration phenomena, ht. 177 cm., wt. 70.5 kg.	13.5	8	60–150			None since adolescence			
	80.0	42	3.5	16,170 mg. Cf. fig. 2 for details	77 wk.	++	+++	+	Face, neck, shoulders, back
	13	10	200	None	4 wk.	Acne faded and disappeared			
3, 26 yr., hypogonad with eunuchoid proportions, ht. 182.5 cm., wt. 84.0 kg.	9.4	31	10			Never before had acne			
	72.0	61	3.5	1,940 mg.	14 wk.	++	++	+	Back, shoulders, face
				None	Several months	Acne quickly faded and gradually disappeared			
				560 mg.	4 wk.	+			
				None	8 wk.	No acne			
				2,100 mg.	15 wk.	++	++	+	
4, 22 yr., hypogonad with eunuchoid proportions and genitalia, ht. 185 cm., wt. 50 kg.	20.5	22	10			Before therapy never had acne			
	66.0	73	3.5	1,940 mg.	14 wk.	++	++	+	Back, shoulders, face
			3.5	None	21 wk.	Acne quickly faded and disappeared			
				560 mg.	4 wk.				
				No treatment		Sebaceous secretions decreased			
5, 43 yr., surgically castrated for 2 yr., castration phenomena present, ht. 172.5 cm., wt. 66.8 kg.	8	28	80			Comedones and eruptions never observed when receiving androgen therapy nor previously during adolescence			
				960 mg.	8 wk.				
				None	21 wk.				
				Pellet implants	5 wk.				
6, 45 yr., surgically castrated for 26 yr., castration phenomena present, ht. 156 cm., wt. 69.1 kg.	3	11	80			No comedones or acne since adolescence			
				2,360 mg.	19 wk.				
				None	22 wk.				
				2,110 mg.	17 wk.				
7, 56 yr., surgically castrated for 13 yr., castration phenomena present, ht. 180 cm., wt. 72.3 kg.	9	5				No comedones or acne since adolescence			
						+			
						+			
8, 27 yr., hypogonad with eunuchoid proportions and genitalia, ht. 177 cm., wt. 72.7 kg.	24	15	10			Never had comedones or acne			
9, 43 yr., spermatic vessels cut in attempted repair of hernia 2 yr. ago; castration phenomena present, ht. 170 cm., wt. 81.8 kg.	23	35	30			None since puberty			
		25							
				2,400 mg.	20 wk.	++	+		Back, shoulders
				None	54 wk.	Eruptions disappeared			
				1,320 mg.	11 wk.	+	+	+	Back, face
10, 18 yr., hypogonad with eunuchoid proportions and small genitalia, ht. 181.5 cm., wt. 81.3 kg.						Never had comedones or acne			

TABLE 2.—*Continued*

Case number, age and status	Urinary excretion per 24 hours			Testosterone propionate		Type of acneform response			Site
	Andro-gens	Estro-gens	Gonado-tropins	Amount	Dura-tion	come-dones	papules	pustules	
	I.U.	I.U.	M.U.						
11, 29 yr., hypogonad with eunuchoid proportions and genitalia, ht. 181.5 cm., wt. 79.4 kg.						Never had comedones or acne			
12, 17 yr., hypogonad with small genitalia, testes not palpable, ht. 174.5 cm., wt. 79.5 kg.	·27	50		1,680mg.	28 wk.	Never had comedones or acne ++	++		Face, neck, back, chest
13, 39 yr., castrated at age of 26, ht. 162.5 cm., wt. 73.6 kg.	11	15		900 mg. None	8 wk. 12 wk.	++ No acne	++		Chest, back

tropic activity was determined by a modification (ratio of uterine weight in mg. to body weight in gm. instead of uterine weight by itself) of the method of Levin and Tyndale (65a). Complete accounts of the technic and results are to be presented elsewhere in conjunction with Drs. Ralph Dorfman and Hubert Catchpole.

Attempts were made to collect in a roughly quantitative manner the material secreted by the sebaceous glands of the face. Later work has shown that unsuspected factors may materially alter the quantity of the secretions. Therefore, the data are not reliable in more than a general way and will be referred to only as increased or decreased secretion. These terms apply to marked change in the oiliness of the skin of a magnitude that can be noted upon gross inspection.

The severity of an acneform response was at first calculated from the number of comedones and papules in the manner of Bloch (9) and as used by Hinrichsen and Ivy (12). As the work progressed, it became apparent that in some cases acne was continually of the highest degree (3+), recorded by Bloch. Adherence to Bloch's classification entailed omission of most of the variations in severity seen in some individuals as *cases 2* and 9, since, despite variation, they would still be 3+. As the present study was directed toward comparison of effects obtained in the same person rather than among different persons, the degree

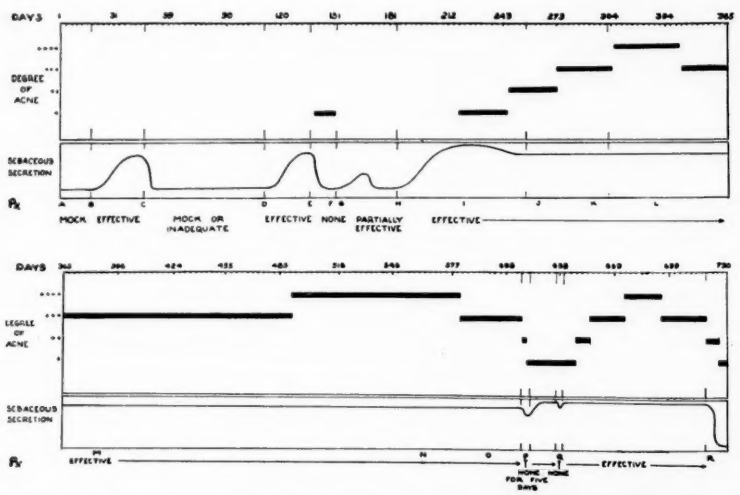

Fig. 2. Parallelism over a 2-year period between acneform eruptions and the administration of male hormone substance to a hypogonad (details in text).

of acne was then estimated in terms of change in severity in the same individual. Severity was judged by the presence, number, size and color of comedones and papules and listed as 1+, 2+, 3+ and 4+. During the study another factor presented itself: resumption of androgen therapy after a brief period of withdrawal produced recoloration of papules that had undergone regression upon cessation of therapy. The present accounts refer to both newly-produced and reactivated eruptions.

RESULTS AND DISCUSSION

VI. Eunuchoid Individuals Do Not Acquire Acne

A satisfactory history was obtained from 7 eunuchoids and corroborated by other members of each family. None had had acne at the usual time of sexual maturity or at any other time prior to treatment with hormone. Incidentally neither did any of this group have furuncles. The continued lack of acne in eunuchoids is analogous to the conditions in early childhood. The undeveloped genitalia, low urinary titers of sexual hormones (table 2) and eunuchoid proportions spoke for continued sexual immaturity. The skin remained soft and fine without comedo or papule. Sebaceous secretions were of limited quantity. Upon cessation of treatment the low urinary levels of gonadal hormones and the disappearance of acne as well as the continued atrophic condition of the testes, argue against any interpretation that the skin eruptions at the time of hormone treatment were due to belated puberty.

Inadequate treatment which did not result in the disappearance of castration signs and in the occurrence of phenomena known to follow administration of androgens (1) was never accompanied by acne.

VII. Acne Accompanies Elevation of Androgenic Levels in Body Tissues and Fluids

A. Effects in boys, eunuchoid and castrate men and ovariectomized women. Following adequate treatment many, although not all, individuals exhibited acneform eruptions. The correlation with satisfactory clinical benefit in eunuchoidism and high levels of urinary androgens, and conversely, the lack of correlation between skin eruptions and inadequate androgenic treatment is well illustrated in table 2.

Boys. Almost all of the boys responded with greater oiliness and coarseness of the skin about the nose. Only 9 failed to develop newly-formed comedones or to exhibit marked increase in the number and size of comedones (table 1). Large comedones were generally confined to the folds and bridge of the nose. Treatment was given for but short periods of time and in limited amounts; so the relatively slight acneform response in comparison with that obtained in eunuchoid and castrate men may be due at least partially to a lesser degree of androgenic stimulation. Papules were observed in only certain of the boys receiving the greatest amount of treatment in preparation for orchidopexy (table 1).

Eunuchoid and castrate men. The 9 eunuchoid and castrate men who received androgenic therapy had markedly increased sebaceous secretions and 6 of the men exhibited many papules or pustule, as summarized briefly in table 2.

The integumental response of *case 2* to the androgenic therapy is given in detail in figure 2. Prior to orchidectomy at the age of 35 years, acne had not been observed for over 13 years. Following the operation sebaceous secretions were greatly reduced and the skin became dry. Ten months later the patient was given mock treatment (at *A* in fig. 2) with no detectable change in the integument. Effective androgen therapy (at *B* in fig. 2) was followed within 10 days by oiliness of the skin and hair, the oiliness being particularly apparent on and about nasal areas. The oiliness disappeared following withdrawal of medication (C) and did not return until after resumption of adequate treatment (D). Then upon continued androgenic treatment a widespread comedo and papular eruption (E) was seen on the back and face on these now oily areas. Therapy was then discontinued for other reasons and the oiliness of skin and hair again rapidly disappeared (F); comedones became less noticeable and the papules lost their redness and shrank in width and in height. Employment of only partially effective treatment (G) resulted in slightly augmented oiliness of the skin surface but this was not marked until after adequate therapy was used (H). With continued medication acne appeared (I) and became progressively worse (J, K, L). Long-continued therapy was accompanied by persistent acne on the face, nape of neck, shoulders, back and area over the deltoid region of the arm. Papules and pustules were numerous, amounting to more than 500 at one time, chiefly on the back and shoulders. Neither induration nor conglomeration of infected follicles was observed. After the application of a hot wet towel to the back, large numbers of comedones could be expressed by the edge of a ruler drawn over the back. Such expulsion of many comedones was followed by a fortnight or more of decreased severity in acneform eruptions. For some variations in the severity of the eruptions (M, N. O) no explanation is offered. Cessation of androgen administration for less than a week (P) was followed by a striking decrease in the severity of the eruptions and in the oiliness of the skin. Resumption of continued treatment (Q) was again accompanied by a reburst of activity in the papules and pustules. These eruptions faded quickly again, along with a

decreased secretion of sebaceous material when medication was discontinued (R).

In different individuals the intervals of time after administration of androgen before the onset of acne or before acquisition of a severe degree of acne are not necessarily of the nature illustrated in the diagram. Even in the same man the responses vary with the dose of hormone, the intervals between injections, the duration of the course of therapy, the previous state of the skin and unknown factors.

One eunuch was never observed to have a papule during several courses of treatment with testosterone propionate that extended over 2 years. The periods of treatment are given in table 2; they are adequate in amount and in duration in comparison with those which induced acne in other patients.

Ovariectomized women. Neither of the 2 women could remember having acne for at least the past 5 years before treatment. In both women the orifices of the follicles about the nose became more patulous and the amount of sebaceous material on the scalp, hair and face was increased. Four small, red papules appeared on the face of one woman, one small papule along the nose of the other woman. The papules remained until the cessation of treatment, whereupon they rapidly disappeared and none were visible a month later. No acne has been noted in the 2 years since the last injection of androgens. Histories as to the severity of pubertal acne in these women did not seem to be reliable.

B. Parallelism between appearance of acneform eruptions and androgenic levels. With alternate periods of medication and no medication, parallel exacerbation of eruptions and then disappearance of eruptions were found. Such alternations of bland therapy with administration of active material were employed in all cases except in the women and in the prepubertal boys; in all but 2 individuals given adequate therapy, medication but not bland treatment was accompanied by induction of skin eruptions. In 3 cases there have been as many as 6 such alternating periods of therapy and mock treatment. This parallelism is further refutation of any interpretation that the integumentary responses were due to belated function of the testes and the patient's own hormone.

The increase in sebaceous secretions was not due to the oily vehicle for the hormone. No increased oiliness of skin or hair was observed in individuals given mock treatment of plain oil for from one to three weeks. More substantial proof that the increased oiliness is effected by the hormone is seen in the augmentation of sebaceous secretions following implantation of testosterone propionate in the form of compressed pellets. No oil was used, yet the parallelism between secretion of sebum and administration of hormone was observed in *case 5* for the period of 5 weeks, after which time the clinical manifestations of stimulation by androgens began to disappear, and concomitantly the skin became less oily and returned to the state observed in the castrate.

It appears incontrovertible that testosterone propionate, a male hormone substance presumably similar to a human testicular hormone (62), is able to produce an acneform reaction in susceptible subjects if present in the body fluids and tissues in sufficiently high and sustained concentrations. Further proof of this relation is seen in the absence of acne in castrate and eunuchoid men, even though many of these individuals are susceptible to acne as revealed upon later administration of testosterone propionate. Comedones and papules disappear upon the cessation of androgen therapy, only to be induced again and again during subsequent courses of treatment with androgen (fig. 2).

Incitants peculiar to the individual may accentuate the acneform response of the patient who receives strictly uniform hormone treatment from day to day. Therefore, exacerbations can occur independently of fluctuation in the amount of hormone present. But no acne, much less exacerbations, occurred when the same dietary or other incitants were employed during periods without androgenic therapy.

C. Distribution of acne. The distribution of acne was chiefly over the face, back and shoulders, and occasionally on the neck and chest and the area over the deltoid muscle. The number of eruptions present at any one time varied from individual to individual and with the amount and duration of therapy. Some individuals had but one or two papules, others more than 200; except for the 3 men with the most severe responses the number of papules was usually less than 50. The pattern of distribution was often roughly symmetrical and the degree of severity was approximately equal on both sides of the body.

Red areas about the base of the hairs were observed on the lower extremities of 3 eunuchoids during receipt of androgen therapy. Pustules and comedones were notable by their absence in these areas. It seems questionable that these red areas were acne in the ordinary sense. It appeared that most of the localized red areas were at the sites of rapidly growing secondary sexual hair.

D. Severity of eruptions. 1. In this series no relationship was observed to color of hair or to previous occurrence of puberty. Sexual maturation prior to treatment with androgens was not a differentiating factor, for generalized acne was observed in *cases 1*, 3 and 4 who had not matured sexually and in *case 2* who was 35 years of age and was the father of two children before operative removal of the testes. Hair color apparently did not in itself reflect the decisive factor, all of the castrate and eunuchoid men under consideration

having black hair save for *cases* 2 and 9 who have dark brown hair.

2. *Relation to amount and duration of hormone treatment.* Severe eruptions were observed in *cases* 1, 2, 3 and 4, but in none of the prepubertal boys. The absence of severe reactions in the boys may be due in part to limited amount and duration of treatment. Such an explanation would not account for the lesser responses in *cases* 6 or 9, however, or the entire absence of response in *case* 5, all of whom received more intensive treatment than *case* 1 who exhibited acne.

3. *Possible relationship to severity of acne previously experienced at puberty.* There is a suggestion of a possible correlation between the severity of the skin eruptions induced by androgen therapy and the severity of the eruptions previously experienced at the time of puberty in that *case* 2 had a disfiguring acne both at puberty and upon androgen treatment; the number and severity of eruptions, especially on the back and shoulders, were considered by both the patient and members of his family to be greater during androgen therapy than during adolescence (from 16 to 21 years). *Cases* 6 and 9 had minor eruptions both at puberty and later upon treatment with testosterone. *Case* 5 had no papules during long periods of treatment and states that at puberty he had noted the entire absence of pustules and papules.

The number of men who had matured sexually prior to castration and androgenic treatment was small and no conclusions could be drawn concerning a relationship between the severity of acne at puberty and that appearing on later treatment. Even such suggestion as is afforded by these data depends upon the recollection by the patient and associates of the degree of acne experienced many years previously.

It should be emphasized, however, that although eruptions were numerous in some patients, in no instance did the severity of the condition approach that encountered in occasional cases at adolescence.

E. Latent period between the administration of hormone and the appearance of acne. The latent period was apparently dependent upon the individual, the duration of treatment, the previous status of the person and perhaps of the sebaceous glands and upon the dose of hormone. The length of time before the appearance of acne showed considerable variability, but papules were observed in *case* 1 within 3 weeks and in *case* 2 within 6 weeks after the beginning of treatment. The individual papule undergoing regression upon interruption of treatment would often show a return of redness and become pustular within a few days following the resumption of androgen injections. This illustrates the error in the axiom first stated by Bloch that only the comedo and never the papule and pustule could be related to the endocrine system. Even when inflammatory and infectious processes exist, the folliculitis depends upon the continued stimulation of the pilosebaceous apparatus by the androgenic substance.

F. Duration of the acneform response. Eruptions continued to occur throughout the courses of treatment which were generally given for only a few weeks or months. In *case* 2 therapy was continuous for one and a half years, acne continuing throughout this period. The severity of the eruptions usually decreased with long continuation of treatment, but exceptions to such a generalization were numerous. It may be significant that with each new course of therapy that followed a period without medication, the acneform eruption became pronounced and then gradually less severe. The analogy to the conditions at puberty is not strict, but the lessening of the response upon continuation of treatment for several months and the exacerbations following each new course of treatment emphasize the possible rôle of variation in the gonadal secretions.

The eruptions persisted in wizened form for as long as 6 weeks after withdrawal of testosterone propionate and were detectable for even longer periods. After the cessation of therapy new papules did not appear. The papules already present remained dark but diminished in size and in color and were not prone to swell or to form pustules. Marked alleviation was seen within one week after withdrawal of medication. The injected hormone may remain in the body and be excreted for several weeks in progressively smaller amounts (63); so the limited persistence of the eruptions after cessation of treatment may possibly be related to resumption of levels of hormone typical of the castrate.

G. Stimulation of sebaceous secretions by androgens. Sebaceous glands distributed over a large part of the body were stimulated upon the administration of testosterone to the patients. The earliest, and with the use of small doses of hormones almost the only, notable increase in secretion occurred on the nose, particularly along the sides of the nose; this response could be detected when treatment was insufficient to induce a widespread acneform response.

Glands associated with the hair follicles on the shaft of the penis secreted material which was retained within the peripheral portion of the pilosebaceous apparatus until the column of secreted substance attained the size, in some instances, of the comedones found elsewhere in the body; these masses were not seen to be extruded spontaneously but some could be expelled by pressure applied to the base of the pilosebaceous apparatus. The small collections of material were easily discernible beneath the skin, lying along the base of the hair follicle as elongated masses about 1 mm. in width, and as much as 4 mm.

in length. They seldom if ever became the seat of papule formation.

The preputial glands of *cases 1, 3,* and *4,* men who had not matured sexually, had not been observed to function. Upon treatment of the patients with testosterone propionate, these glands secreted soft, white, odoriferous material. *Cases 2* and *9,* castrates, exhibited a similar activation of the preputial glands during periods when receiving injections of testosterone propionate. Upon cessation of therapy, 2 of the patients complained of dryness and cracks in the skin of the inside surface of the prepuce. Both of the ovariectomized women described the occurrence of increased secretions of the vulva, but the extent and nature of these secretions were not determined.

The areolar glands of Montgomery were observed to be definitely more prominent in only 2 of the men receiving treatment. No biopsies were made and the nature of the change is not known.

When without treatment some patients experienced a feeling of scratchiness upon winking, but this was not ascertained to be due to decreased secretion of the tarsal glands. It is interesting that wax secretion of the ceruminous glands, which are modified sweat glands, was stated by the patients not to be noticeably affected.

H. Reactions to dietary factors and to acne inducing agents like paraffin oil applications. Diet was claimed by the patients to influence the severity of the skin eruptions in *cases 2, 3* and *4.* A large amount of carbohydrates and chocolate, usually along with overeating of other foodstuffs, was reported to be followed shortly by an increased number of swollen, colored papules. Allergy to special foods was not reported.

In an attempt to investigate the reactions of the sebaceous glands, paraffin oil was kept in continual contact with a designated area of the skin of the back during periods of one week when the patients received, respectively, treatment and no treatment. No demonstrable results were observed, but longer periods of time and other agents than paraffin oil must be employed before conclusions can be drawn.

I. Similarity to naturally occurring acne. The acne known to result from the presence of androgens shows a close similarity to naturally occurring acne in patients never given endocrine treatment. This similarity will be stressed at a later time after completion of wax model reconstructions from serial microscopic sections of androgen-induced and naturally-occurring eruptions.

VIII. Levels of Androgenic, Estrogenic and Gonadotropic Substances in Body Tissues and Fluids

Studies have been made which allow some degree of comparison between patients with and without acne. Urine has been examined for estrogenic, androgenic and gonadotropic material, blood for estrogenic substances.

A. In patients without acne: prepubertal children, eunuchoid and castrate men. In prepubertal children acne is not common until the titers of sex hormone substances have shown appreciable increase.

In eunuchoid and in bilaterally orchidectomized men the titers are represented in table 2. These data are in agreement with previously published reports of the output in these types of individuals (63, 66, 67).

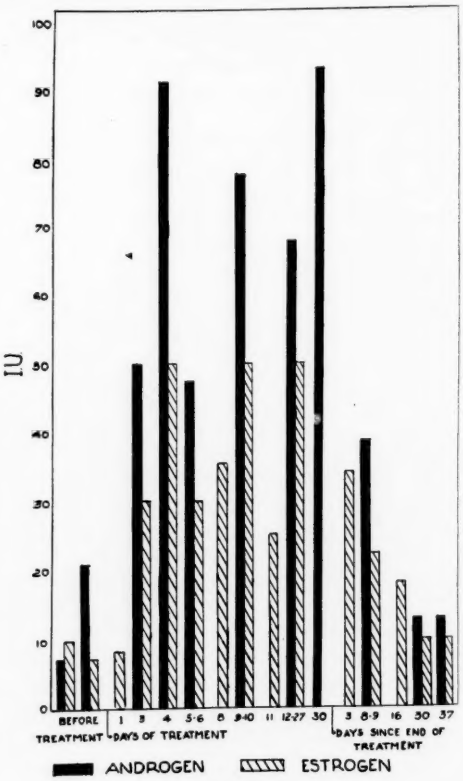

Fig. 3

Figs. 3 to 8. (Determinations of urinary androgens and estrogens made in collaboration with R. I. Dorfman). Absence of an acneform response in some men treated with androgen is not due to complete failure to react to the hormone. Levels of both androgenic and estrogenic activity in the urine of castrate and eunuchoid men increased during courses of androgenic therapy in a like manner whether or not the man acquiring acne; figures 3, 7 and 8 are of individuals who developed acne, figure 5 of one who did not respond with acne. All 4 men had low levels of urinary androgens and estrogens before treatment and during the standard course of therapy (20 mg. of testosterone propionate daily) exhibited levels within the range of normal men.

The ratio of androgen: estrogen calculated from figures 3 and 5 and shown in figures 4 and 6 is not higher in the men who developed acne, this would not support claims (71) that a high ratio per se is responsible for acne.

The urinary levels of estrogenic and androgenic substances are low. This data would not by itself selectively implicate the low level of either androgens or estrogens as responsible for the absence of acne. As the relative amounts of androgens and estrogens in some hypogonads are about those of normal men, and in other cases quite dissimilar, it would seem that the ratio of androgens to estrogens may be immaterial from the standpoint of acne, at least when the quantities are small.

Follicle stimulating gonadotropic substance may be present in either large or small quantities without being accompanied by acne. In the absence of therapy, *cases 1, 3, 4* and *8* have less than 10 M.U. per 24 hours, *cases 2, 5, 6* and *9* from 80 to over 200 M.U. per 24 hours. None of the patients exhibited acne, unless androgens were administered. The fact that acneform eruptions in some of these men were induced upon elevation of the amount of androgens in the body indicates that they were capable of responding with acne but that extremely high or low levels of follicle stimulating gonadotropic substance did not induce acne.

B. In patients who acquire acne upon androgenic treatment. Of the patients with low levels of sex hormones, certain ones acquire acne upon receipt of androgenic therapy. Attempts were made to ascertain whether or not an acneform response was correlated with differential changes in the levels of urinary hormones or with the capacity of the individual to show reactions that are held to be influenced by androgens (1).

Changes in the hormone content of the urine of such patients are presented in table 2 and in figures

TABLE 3. ANDROGENIC AND ESTROGENIC SUBSTANCES IN THE BLOOD AND URINE OF PATIENTS WITH AND WITHOUT ACNE

Authors	Number and sex of subjects		Age	Urine extraction and assay	Daily levels of				Remarks
					Estrogens		Androgens		
	Normal	Acneic			Range	Av.	Range	Av.	
			year		I.U.	I.U.	I.U.	I.U.	
Wile, Snow & Bradbury (1939) (69)	6♂		18–21	Continuous extraction. Bioassay with capons and spayed ♀ rats			49–140	87	
	4♂		18–21		40–200	97			
		9♂	16–20				59–176	100	
		8♂	16–20		30–150	56			
	6♀		16–21		100–200	160	18–80	44	
		10♀	16–21				30–94	57	
		9♀	16–21		50–200	120			
Wile, Barney & Bradbury (1939) (69)	20♀		15–21	Continuous extraction; bioassay with spayed ♀ rats	5–12 (R.U.)	3.7 (R.U.)			Does not represent total extraction of estrogens
		12♀	15–21		7–7 (R.U.)	4.1 (R.U.)			
Cornbleet & Barnes (1939) (70)	7♀			Continuous extraction; bioassay with chicks			19–40	30	
		7♀					12–26	19	
	2♂						40	40	
		4♂					12–30	20.2	
Lawrence & Werthessen (1940) (71)	8♀			Continuous extraction; colorimetric assay of androgens; estrogenic assay with ♀ rat	250–850	370	47–164	89	All patients with acne had severe dysmenorrhea; for technical reasons androgenic values are not expressed as mg. or I.U.
		8♀			60–130	120	36–113	79	
Rosenthal & Kurzrok (1933) (72)		34♀	11–20						Variation in estrogenic excretion in different parts of cycle not taken into account at this time

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3 to 8. In general the data in figure 3 are representative of the urinary hormone levels found upon treatment of such men (58, 63, 67) and are not peculiar to men either with or without acne. It will be seen that upon treatment of the patients with androgens the quantities of urinary estrogens and androgens were greater and may lie within the limits observed in normal young men (64). Acnegenesis does not appear to require postulation of abnormally high quantities or peculiar quality of the androgen but rather the presence of effective androgenic levels in body tissues and fluids. Probably the excreted hormones are qualitatively similar to those excreted by the normal man, since the estrogen is phenolic like members of the estrone series, (59) and the androgen largely androsterone, urinary androgen of the normal man (62, 67, 68).

The relation of androgenic therapy to urinary levels of follicle stimulating gonadotropic substance is tabulated in detail in table 2 from which it is further apparent that changes in the titer of this gonadotropin were not instrumental in the formation of acne.

Thus, in patients who received androgenic therapy, urinary levels of both androgens and estrogens rise to approximate normal amounts, in both absolute and relative quantities, and seemingly resemble qualitatively those in the urine of normal men. As increased amounts of urinary sex hormones occur in both the patients who do and do not develop acne, the inescapable conclusion from the present data is that androgen therapy produces increased levels of urinary sex hormones but that such responsiveness to androgen as measured therein is not the sole factor in determining which patient will exhibit acne.

C. *In patients with acne* (table 3) 1. *Androgens.* In contrast to the low urinary levels of androgens in eunuchoids, who are individuals without acne, high levels of androgens are reported in patients with acne. Wile, Snow and Bradbury (69) found that the daily androgenic secretion in the urine of 6 normal men amounted to from 49 to 140 I.U. with an average of 87 I.U.whereas in 9 men of a similar age range who had acne, there were from 59 to 176 I.U. with an average of 100 I.U. In 6 normal women the excretion was from 18 to 80 I.U. with a daily average of 44 I.U., and in 10 women of the same age range, who had acne, from 30 to 94 I.U. with a daily average of 57 I.U.

In contrast to these results Cornbleet and Barnes (70) reported from 19 to 40 I.U. of androgenic activity daily in the urine of 7 normal females, 40 I.U. in 2 normal males. In 8 females with acne there was from 12 to 25 I.U. daily, in 4 males with acne from 12 to 30 I.U. daily. The ages of the patients were not stated.

Lawrence and Werthessen (71) state that values for urinary andrógens are higher in patients with acne, but the difference from values of control patients is not pronounced (table 3).

The range of values is understandably variable among laboratories because of the use of different technics in the collection and assay of urine. Yet values from the same laboratory should permit comparison between normal individuals without acne and patients with acne. It is notable in this regard that Wile, Snow and Bradbury (69) found higher andro-

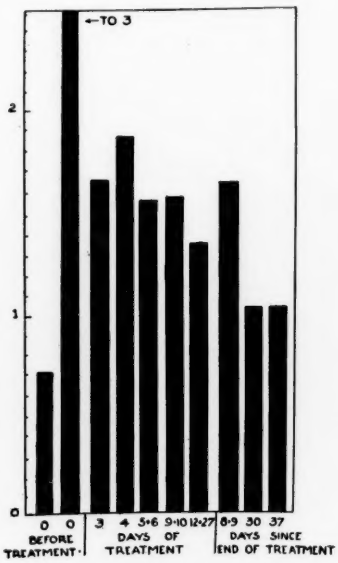

Fig. 4. See legend for figure 3.

genic values in the patient with acne than in the normal individual, whereas Cornbleet and Barnes (70) did not observe such a difference. Additional information on this matter is necessary. More attention should be paid than in the past to the type of patient under study. For example, inclusion of the eunuch or eunuchoid as an individual without acne is misleading and would tend to give low androgen and estrogen values in the non-acne series. Conversely, inclusion of patients with adrenal virilism in a series of patients with acne would mean study of persons with very abnormal reproductive function and, especially if colorimetric assay is carried out, distortion of the mean average by addition of a few cases with markedly elevated androgenic levels. Patients with these endocrine abnormalities are cases for study in themselves but hardly a fortunate choice for determination of differences in hormone levels between average individuals who do or do not have acne.

Valuable information might be gathered from com-

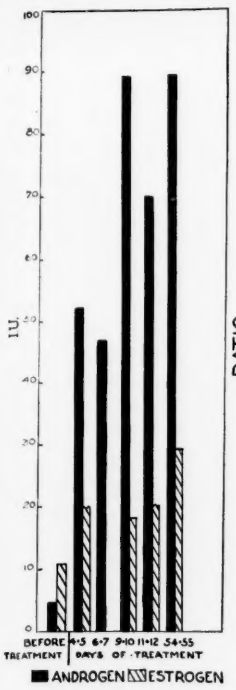

Fig. 5

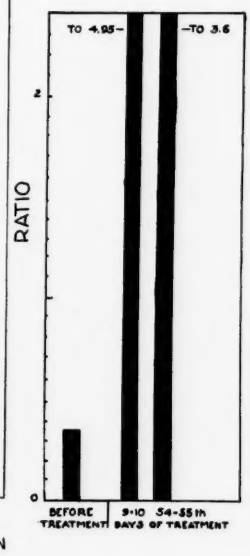

Fig. 6

See legend for figure 3.

parison between assays of sex hormones in the urine and the onset of and degree of acne in prepubertal and pubertal children, especially if study of the same individuals could be extended over several years.

2. *Estrogens* (table 3). Apparently levels of estrogenic substances in blood and urine are low in patients with acne. Rosenthal and Kurzrok (72) found that in 34 females with acne, whose age was from 11 to 33 years, estrogen was not detected in the urine (amount not stated) of 27 cases, but was present in 6 instances in amounts found in normal women. Since the quantity of estrogenic substance varies with different phases of the menstrual cycle (73), Rosenthal and Neustaedter (74) repeated this general type of observation by assaying blood samples taken the last week before menstruation. During this portion of the cycle Mazer and Goldstein (75) had obtained positive assays (1 M.U. or more) from 40 cc. of blood in 85% of normal women. Frank and Goldberger (76) had found in 40 cc. of blood 1 M.U. or more in 44% of 18 normal women tested from the tenth to the third day before menstruation; in 100% of 13 women from the third to the last day before menstruation Rosenthal and Neustaedter (74) state that they had obtained 1 M.U. or more of estrogenic activity in 75% of an unstated number of normal women evidently from about the tenth to the last day before menstruation. With these figures as standards they (74) compared the estrogenic values obtained from 40 cc. of blood from each of 29 females with acne from $11\frac{1}{2}$ to 34 years of age; only 7% gave an assay equal to or greater than 1 M.U.

Wile, Barney and Bradbury (77) extracted estrogenic substances from the urine of 20 normal women between 15 and 21 years of age and of 12 women of a similar age who had acne. They recognized that the extraction of estrogens was not complete at the low acidity used and stated that the values of 7.7 R.U. for the normal and 4.1 R.U. for the acneic women represented free rather than total estrogenic substance. Therefore, Wile, Snow and Bradbury (69) repeated similar investigations using better procedures. Six normal women from 16 to 21 years of age excreted from 100 to 200 I.U. daily with an average of 160 I.U., whereas 9 women from 16 to 21 years of age, who had acne, excreted from 50 to 200 I.U. daily with an average of 120 I.U. Four normal men from 18 to 21 years of age excreted from 40 to 200 I.U. daily with an average of 97 I.U.; 8 men of from 16 to 20 years of age who had acne, excreted from 30 to 150 I.U. daily, with an average of 56 I.U.

Low levels of estrogens in patients with acne are

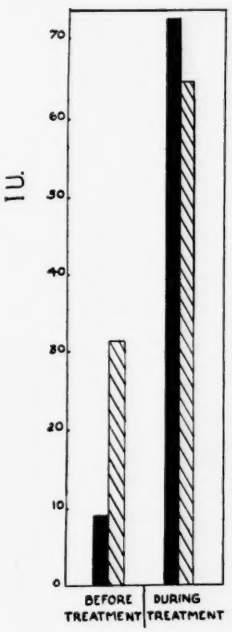

Fig. 7

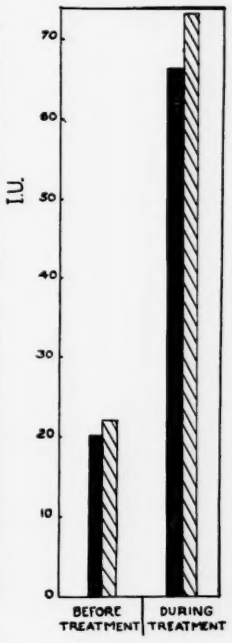

Fig. 8

See legend for figure 3.

probably not in themselves responsible for stimulation of sebaceous secretion. In support of this statement it can be noted that the eunuchoid has lower levels of estrogens than the individual with acne. So the diminished estrogen levels are not the primary event in acne production. There is the possibility that this decrease is a secondary phenomenon resulting from the presence of elevated levels of androgenic substances in the tissues and fluids of the body, it being known that androgens can suppress both the production and some of the actions of estrogenic substances; discussion of the subject of antagonism is omitted for the sake of brevity and also because the extent and mechanism of the antagonism are not well understood. Claims that a disturbed ratio is responsible for acne (71) would not receive support from the much greater range of ratios in eunuchoid and castrate men who do not have acne.

3. *Gonadotropic substances.* McCarthy and Hunter (56) interpreted their measurements of estrogenic and gonadotropic substances as indicative that the function of the anterior lobe of the pituitary or of the gonads was deficient in many persons with acne. Wolf (78) has commented without giving data that "other possible endocrine influences have been traced in seborrhea, chiefly relating to *gonadal hypofunction* [Wolf's italics], either primary or secondary to pituitary inactivity." Obviously the conclusions of these men are contradicted by the present study, which emphasizes the induction of acne by androgens. Acne can be present without direct relation to levels of gonadotropic and estrogenic substances and needs no postulation of hypopituitarism and hypogonadism.

4. *Comment.* The inference drawn by the author from studies of levels of gonadotropic and sex hormones in blood and urine, is that acne is directly related to effective levels of androgens in the acne-susceptible individual. Gonadotropic (follicle stimulating) substance is not directly at fault and estrogens may be at normal or at low levels.

IX. Mechanisms Whereby Androgens Might Produce Acne

Androgens exert several actions which may be examined in an attempt to account in part for the production of acne in susceptible persons. In the integument they result in an increase in vascularization (quantity of blood, content of oxy-hemoglobin and possibly rate of blood flow), pigmentation (melanin and hemoglobin), retention of salt and water (possibly nitrogen) and stimulation of sebaceous secretions. These actions may be more closely interrelated than now realized and they may be in part expressions of underlying fundamental processes, as, for example, the metabolism of a part controlling its blood supply. Further, the reactions in the skin are in all probability vitally affected by changes in the rest of the body. Experiments undertaken thus far do not allow conclusions to be drawn as to whether the acneform response to androgenic substance is due chiefly to local effects in the skin or to more general effects in the body as a whole.

Increased vascularization of the skin upon the administration of androgens has been demonstrated in castrate and eunuchoid men (1, 79) in whom an increased amount of oxy-hemoglobin is detected spectrophotometrically within an hour after injection of hormone substance. A similar effect has been demonstrated (80) following the administration of estrogens.

Adrenal cortical hormones, androgenic, estrogenic and luteal substances cause a retention of salt and water (81, 82). This matter is of undoubted importance, and may be of significance in acne seen near the time of menstruation, but it cannot be fully examined here other than to call attention to the effect of hydration upon inflammatory processes in the integument (83, 84). Stokes, Beerman and Ingraham (85) have attempted in critical fashion the difficult evaluation of the influence of these effects upon infection.

The existence of a seborrheic action by androgens is indicated by the observations in this paper. This may be derived from a direct action upon the sebaceous glands or indirectly through increased vascularity, hydration of the tissues, fat metabolism or other processes. There may well be other than androgenic factors in seborrhea; in this connection it might be recalled that there is evidence that the nervous system exerts some manner of control over the sebaceous glands (86, 87).

Augmented activity of the sebaceous glands may also account in part for the epithelial hyperplasia claimed to encircle the neck of the follicle involved in acne. Hass (88) has shown that epithelial hyperplasia can be a reaction to the presence of lipids. Subcutaneous injections of oils (olive and cod-liver) induced "frequent proliferative reaction." "The cellular activity occasionally results in partial epithelialization of the cysts. . . . "

The skin assumes a coarse and roughened appearance upon treatment of hypogonadal patients with androgens. After the cessation of treatment, some patients exhibit peeling of the outer layers of the epithelium. Desquamation may extend over most of the body save the cornea and possibly the soles of the feet and palms of the hand. The extensiveness of this peeled layer was commented upon, in the 3 patients in which it was observed, as "moulting" or "shedding skin like a snake." Increased coarseness of the skin and desquamation of outer layers of epithelium after withdrawal of androgenic therapy are not

proof that testosterone propionate stimulates epithelial hyperplasia. Cell counts of the epithelial layers in numerous biopsies taken during periods during and without medication would provide some evidence, but would require more biopsy material than is available at present. Perhaps desquamation of the skin is occasioned by dryness from decreased sebaceous secretions.

Changes in the levels of androgens in the body tissues and fluids may provide a technic with which to probe the mechanism of acne formation. Two of the eunuchoid and one of the castrate men, who responded with severe acne to long periods of treatment, exhibited a particularly pronounced reaction during the first rather than the latter portion of treatment. This might be interpreted in several ways. With further data, it may prove to be an artifact, or it may be that at the beginning of treatment, secretion of sebaceous material is augmented without adequate excretion. Whatever the mechanisms involved, it would appear that the follicular responses change in character during continued treatment of the patient with the same dose of hormone, acne generally becoming less severe in time. Presumably this is due to better adjustment between the secretory and excretory capacities of the follicles, but no conclusion is warranted in the absence of analyses over long periods of time of the amount and type of secretion, body fat metabolism and other relevant data.

The problem posed by continuation of some degree of eruption while androgenic therapy is maintained (for 16 months in one instance) calls for explanation. As with one exception adequate treatment was maintained without interruption, this is scarcely a series of responses to the beginning of a period of medication such as are found with intermittent medication. Do certain follicles begin to secrete only after long latent periods? Or do follicles with previously normal function form comedones or become acneform at later dates?

It is important to note that a single papule may persist for long periods of time, even months. The eruptions in naturally occurring acne might well be reexamined from the standpoint of the persistence and character of changes in individual eruptions. Attention to these details would allow closer approach and perhaps clues to the mechanisms involved in acneform eruptions.

X. *Role of Androgens in the Incitation of Acne*

The above observations show that androgens are capable of inciting acne. The clinical states accompanied by acneform eruptions are examined below in an effort to evaluate the possible rôle that androgens may play in the induction of acne observed clinically in what might be termed physiological (puberty, menstruation) and pathological (adrenal virilism, arrhenoblastomata) states.

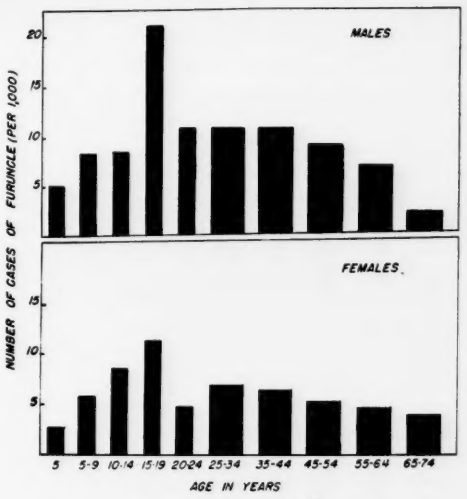

Fig. 9. (Drawn from data supplied by Mr. Selwyn Collins of the United States Department of Public Health.) Somewhat similar in nature to figure 1 of the incidence of acne, is the relationship to adolescence of the incidence of furuncles among males and females. The incidence is highest at the time of adolescence and greater in boys than in girls; in conjunction with details described in the text these facts suggest correlation with the presence of male hormone substances.

A. In males. Salient facts are (1) the absence of acne in males with markedly sub-normal testicular secretion and the presence of increased sebaceous secretions plus acne upon elevation of androgenic levels in the body tissues and fluids of these individuals, (2) fluctuation in the acneform response with the degree of androgenic stimulation of the individual and disappearance upon decrease in the effective body levels of androgens and (3) some lessening of the severity of the eruptions upon long-continued injections of testosterone propionate. These facts may have some relationship to the conditions affecting acne during adolescence. With the onset of sexual maturation male hormone substances are provided in greater quantities and may be a factor in the induction of acne in both boys and girls. An indication of the pertinence of this correlation should be afforded by comparative studies of acne and the urinary excretion of sex hormones in pubertal children. It is perhaps not irrelevant that males exhibit both a greater severity of acne (9) and higher levels of urinary androgens (64) than females.

In precocious puberty acne might also be expected in accordance with the present postulation of acne inciting properties by androgens. No case has been adequately studied with regard to acne and the endo-

crine condition; so comparison cannot be made with the eruptions seen at the usual chronological ages save to state that acne in the boy with precocious puberty may be severe (89), and may occur in a child one year of age (90).

B. In females. 1. *At puberty.* The incidence of acne in adolescent girls may be related to the onset of gonad function; the urinary androgenic activity of the adult females is about two-thirds that of the male (64) and it is at the time of sexual maturity that urinary levels of androgens become elevated. In the data presented in this paper the female is shown to be able to respond to testosterone with comedones and papules. Precocious development of adult characteristics of a masculine nature in the girl with an adrenal cortical tumor may be accompanied by pronounced acne (91, 92). In the following paragraphs evidence is presented that acne may occur in the female in other conditions in which androgenic levels may be increased; the titers of estrogens may be low, which would not indicate that estrogens induced the acneform response in these individuals.

2. *Near the menstrual period.* In women with periodic acneform eruptions no measurements have been published of the androgen levels throughout menstrual cycles nor is there as far as the author has been able to find, a detailed or even satisfactory account of the length of the cycle, the onset and duration of the periods of bleeding, or other data pertinent to comparison with normal women. Daily determinations of urinary sexual hormones throughout the menstrual cycle have been made in only a very limited number, 4, of normal women for only one cycle (64). Interpretations do not seem warranted at present. Since the data of the present paper do not prove that androgens produce acne but rather that they may augment sebaceous secretions and that acne may result, the acne observed near the time of menstruation may be precipitated by other factors than androgens.

3. *In adrenal virilism.* Acne is not uncommon in women with virilism accompanying a tumor or hyperplasia of the adrenal cortex. In these cases the urinary levels of estrogens are often low, the levels of androgens in some instances higher than in normal women (66, 93–97). In severe acne accompanying virilism in a patient with marked masculinization, urinary androgenic levels were within the range for normal women. The low estrogen titers in these cases may be of significance (66), possibly in representing almost unopposed action of the androgens. Other explanation of the low urinary androgenic levels despite pronounced masculinization may be offered to the effect that steroid metabolism is deranged or that bioassay of urinary androgens does not reflect the body condition. Whatever the explanation, there coexist acne, hirsutism, masculinization, low titers of urinary estrogens, normal or high titers of urinary androgens.

The enormously high titers of urinary androgens occasionally found in adrenal virilism represent metabolism of androgenically active material of a nongonadal origin, Callow being of the opinion that adrenal androgens are the source. Testosterone, a hormone isolated from the testis (of the bull), is apparently not broken down to dehydroisoandrosterone in any material amounts (68); so it would seem that an androgen other than testosterone was concerned in the adrenal virilism in which great amounts of dehydroisoandrosterone have been isolated from the urine. Reichstein (98) has isolated adrenosterone and desoxycorticosterone from adrenal tissue; the former has definite androgenic properties. Further proof of a non-gonadal source of androgens in at least certain cases of virilism is deduced from the masculinization seen after bilateral oöphorectomy (99, 100).

Folliculitis seen in cases diagnosed as pituitary basophilism may be considered in general in the same manner as in adrenal virilism, especially since the distinction from cases with known adrenal involvement may be held to be questionable.

Similarly the only 3 cases of hirsutism charged to thymic tumors, of which the author is aware, have all been shown also to have adrenal hyperplasia (101, 102).

4. *In women with arrhenoblastomata.* Acne is mentioned in only an occasional report of arrhenoblastomata (103) but close examination of photographs of the reported cases reveals unmentioned skin eruptions that appear to be acne (104). In view of the hirsutism, enlargement of the clitoris and other changes of a masculine nature it is not illogical in view of the concept advanced in this paper to expect acne in some of these individuals. Since acne has never been regarded as related to androgens, acne might be omitted in descriptions of known signs of masculinization.

C. Nature of the androgenic substances that induce acne. The present data indict testosterone acetate and propionate as inductors of acne. Methyl testosterone in doses of 70 mg. daily was accompanied by acne in one of two eunuchoids so treated (unpublished data). Less conclusive circumstances suggest that non-gonadal androgens may be concerned in acneform eruptions in adrenal virilism. It is possible that seborrheic action may also be exhibited by more than one adrenal cortical hormone and in steroid metabolism by intermediate compounds possessing androgenic activity.

Androsterone induces vascular and seborrheic changes in the skin and influences erectile capacity of the penis; androsterone has not been administered

to patients in doses and intervals sufficient to test its ability to induce acne, but its androgenic properties observed during short periods of trial and the similarity of its actions to testosterone suggest that acne might follow the continued use of androsterone. If the acne inducing properties run parallel to the androgenic activity, quantities much larger than those of testosterone would be required.

Since many compounds possess qualitatively similar androgenic properties, it seems logical that several of these compounds might be capable of stimulating sebaceous secretions. Until future investigations reveal the nature and effects of the various androgens in the human body, testosterone can be considered as possessing exemplary properties in stimulating sebaceous secretions, and androgens tentatively to be a generic group that may act possibly as seborrheic agents and be prime factors in the induction of acne.

XI. Rôle of Estrogens and Other Hormones in Acne

Despite a correlation between acne and androgens there is no proof that all forms of acne are caused by androgenic substances. Other substances may exert a similar effect, and factors besides the mere presence of androgens in effective quantities are undoubtedly of major importance. It is unfortunate that detailed studies have not been reported of the integument in women with sexual underdevelopment, nor of the responses of the skin to the use of estrogens. Several gynecologists, who have employed estrogens extensively in prepubertal girls and in eunuchoid and oöphorectomized women, affirm that they have not observed acne following extended treatment with large doses of estrogens or progesterone (personal communication from R. Kurzrok, U. Salmon, E.Shon and R. Lewis).

If not directly, estrogens may influence sebaceous secretions indirectly, for there is an antagonism between androgens and estrogens whereby the one tends to suppress some of the actions of the other group. Antagonism of estrogens to the seborrheic action of androgens has yet to be investigated, but demonstration of other counteractions between these two types of substances has served to elucidate some of the checks and counterbalances of these hormones which co-exist in tissues and fluids of the body.

Caution must be exercised, however, in attempts to correlate acne or lack of acne with measurements of the relative levels of urinary androgens and estrogens. The level of urinary hormones may not necessarily provide an exact index of the level of body hormones (63) and in some instances is somewhat in the manner of imperfect mirror writing of past events. The need for more than mere bioassay of the total androgenic excretion in the urine is especially evident. Studies of the nature and quantities of both active and 'inactive' steroids might be enlightening.

Fat and sterol metabolism of the integument and the body are extremely enticing approaches to the pathogenesis of this condition, as it is unlikely that profound integumentary changes are unrelated to general body metabolism. Certain effects of the body lipids upon sebaceous secretions which have been reported by Pembrey (105) are provocative.

It must be remembered that thus far the only definitely known incitant of acne is androgenic substance which must be present in adequate amounts and over a sufficient duration of time. At present no other substance is known to be capable of inducing acne if levels of androgens are low, as in eunuchoids. Future work may provide delineation of other incitants of the pilosebaceous apparatus and coordination with bacterial and immunological factors.

XII. Rôle of Sex Hormones in Responses of the Skin Other Than Acne Vulgaris

A. Other acneform eruptions. No patient in the present series has exhibited acne of a rosaceous or varioliform type. Since acne other than the common type is apparently also dependent upon functional pilosebaceous apparatus, it might be expected that there too, some stimulator of sebaceous secretion would act prior to formation of the papule and pustule. This is obviously the case in those eruptions with a fatty core. Androgens and other agents that incite sebum formation may thus play a primary rôle in conditioning the follicle and adnexa to such later processes as are compatible with the constitution and environment (infection, diet, etc.) of the individual. Sebaceous cysts, rhinopyma and sebaceous adenoma must logically be subjected to examination from this viewpoint.

B. Furuncles. It may be more than coincidental that none of the series of eunuchoid but all of the castrate men described in this paper had a furuncle before treatment with testosterone propionate. Three of the patients developed one or more furuncles during treatment with a male hormone substance No furuncles appeared during periods when androgenic substances were not administered, although most of the patients had no treatment during a large portion of the years while under observation. Admittedly, the evidence regarding a possible correlation between androgenic stimulation of the patient and the onset of furunculosis is vague and not sufficiently reliable to be trustworthy. Without minimizing the extreme importance of infections the present observations suggest that in many forms of folliculitis a basic factor may be the sebaceous secretagogue, and possibly to some extent the stimulant to growth of

certain hairs; this factor is supplied in part at least by androgens. Experience serves to indicate that the greatest incidence of furuncles and carbuncles is found during adolescence or later and that the most frequent involvement is the second and third decades. Mr. Selwyn Collins of the United States Public Health Service has kindly placed at the author's disposal data concerning the incidence of furuncles. This is represented in figure 9 where it will be observed to be similar to the type of curve drawn for the incidence of acne (fig. 1). The occurrence predominantly in males, and at the time of adolescence in either sex, is in accordance with a possible relationship to androgens.

C. Other responses. Inspection of the present data raises questions of immunological and dermatological differences between the mature and immature individual. One might inquire to what extent, if any, the changes in the skin induced by androgens, such as retention of salt and water, augmentation of vascularization, sebaceous secretions and formation of pigment, allow responses different from those of the immature individual. Along with the changes produced by sex hormones in lymphoid organs and in the general body status, the skin may possibly acquire, under the influence of these substances, a potentially different response over and above the presence or absence of folliculitis.

Finally, the response of the integument to irradiation, infection, trauma and to thermal and a host of other impinging forces may be in part conditioned by such agents as androgens. Unna (p. 198) (17) states "The preference of cutaneous horns for the seborrheic regions of the skin, the scalp, forehead, the nose, the eyelids, the glans, and the scrotum is somewhat remarkable; as is the seborrheic history of many of them." Sutton (106) makes the comment that "Seborrheic keratoses are the most frequent of all forerunners of prickle-cell cancer of the skin."

XIII. Treatment of Acne

With establishment of the fact that androgenic substances are able in at least certain individuals to incite acneform eruptions and with the intimation that they may play significant rôles in naturally occurring acne and that they (or other substances) may be prerequisites for acne, the modes of treatment may properly be examined. Yet full understanding and proper therapy must await detailed knowledge of pathogenesis.

If the mode of pathogenesis outlined in this paper is sustained and confirmed, it would appear that primary events in the acneform response to testosterone are the secretion and later retention of sebaceous materials by follicles. It is debatable at present that the effect of closure of the neck of the follicle by epithelial hyperplasia in itself is more than superimposed upon the sequelae of sebaceous secretion. Similarly, growth of bacteria within the follicle may be secondary to the secretory activity of the glands. The question of excretion of irritants by the glands is not disproven and one cannot be certain that the first products of secretion are not atypical, whether or not they are toxins or irritants.

Thus the problem apparently centers about the most suitable and efficient manner of obtaining a balance between secretion and excretion. Conceivably this could be done by procedures which would either maintain an open aperture of the follicle and the passage of secretions or restrain fulminating processes of secretion. The usual methods of treatment described in dermatological treatises will not be discussed here, but if the present observations prove to be correct, they will perhaps bear critical study as to the manner in which they may best promote a satisfactory adjustment of follicular secretion and excretion. Proper treatment should, however, extend to considerations of diet, metabolism, infection and other factors besides gonadal secretions.

A. Treatment with androgens. In the first report of an eunuchoid treated with testosterone for sexual underdevelopment (1), therapy was given for a month; this was followed by a rest period of 7 weeks and then by administration of first of low and later of more adequate treatment with testosterone. Acne appeared only after a latent period and became pronounced only by the end of the period of injections. Toward the end of the rest period the acne tended to disappear. When small amounts of androgen were again given, the acneform response was again increased but as treatment was continued (with larger doses) the severity of the eruptions was diminished. One interpretation of these results is that acne appeared most severely when the level of androgens was below normal but still not that of the castrate. Another would emphasize the condition of the pilosebaceous apparatus and the period of time during which it is acted upon by the hormone substance; this latter interpretation now seems the more tenable.

Since the report of the above case several studies have been made of the effect of testosterone upon patients with functional gonads and acne. Molitch (108) gave injections 3 times weekly to 12 males between the ages of 16 and 23. The doses employed were 5 mg. for the first month, 10 for the second and 25 mg. for the third month. There was some improvement in certain cases but only equal to that exhibited by a control group of patients who received no hormone treatment. Milco (2) has observed the appearance of acne upon continued administration of testosterone propionate to a man who had presumably low levels of androgens. His case is similar to that reported before (1) and those in the present paper except that the acneform eruption appeared after injections of but 5 mg. of testosterone propionate twice weekly for a month. Reichert

TABLE 4. SUMMARY OF RESULTS OBTAINED WITH GONADAL AND GONADOTROPIC HORMONE SUBSTANCES AS THERAPY FOR ACNE

Author	Number, sex and age	Endocrine treatment	Dose and period of treatment	Results	Remarks
van Studdiford (1935) (111)		Des. ovarian and orchitic extract			Probably much of the material without activity
Michael (1935) (11)					Data not fully presented; usefulness of estrogen then available to be limited
Lawrence (1936) (112)	10♂, 9 yr. 19♀, 18 yr.	APL gonadotropin	2 cc. every other day; av. dose 3,360 R.U.	10 cured 11 much improved 7 some improvement	Author termed results favorable; control data would be valuable
Rosenthal (1937) (113)	38♀ 13–33 yr.	Estrogen, APL gonadotropin	50 R.U. daily, followed by daily inj. of 100 R.U. APL	15 not improved 10 sl. improvement 13 improved	Author feels that results are somewhat favorable; control data would be valuable
Rosenthal (1937) (113)	2♂ 17 & 18 yr.	APL gonadotropin	100 R.U. 3×wk. for several weeks	1 not improved 1 improved	
McCarthy & Hunter (1937) (56)		APL, Theelin	2 cc. 3×wk. for 3 mo. then 2,000 I.U. 3×wk. for 3 mo.	No effect	This therapy of little use
Williams & Nomland (1937) (114)	20 students, av. 19 yr. 19 (28♀; 11♂)	APL gonadotropin Sterile water	2 cc. 3× wk. for 8–11 wk.; av. dose 5,700 R.U. 3×wk. as above	10 improved 7 some improved 3 none improved 9 improved 6 moderately improved 4 slightly or not improved	Little therapeutic benefit
Templeton & Truman (1938) (115)	9 boys & 8 girls 22 young women	APL gonadotropin Estrogen	200 R.U. 3×wk. av. course 10 wk. 2,000 I.U. 1×wk. av. course 9 wk.	10 not improved 7 improved from 33 to 66% 11 not improved 11 improved from 33 to 66%	Authors feel that results are inferior to those obtained with x-ray treatment
Molitch (1938) (108)	12♂ 16–23 yr. 10♂ 17–20 yr.	Testosterone propionate Bland oil	5 mg. 3×wk. for 1 mo.; 10 mg. 3×wk. next month; 25 mg. 3×wk. next month	6 improved 6 not improved 6 improved 4 not improved	No benefit
Cornbleet & Barnes (1939) (70)	46	Testosterone propionate	10 mg. 1×wk. for 3 mo. or more	24 improved by 50% 9 eruptions disappeared; relapse in 5 upon cessation of treatment; improvement in 3 upon later treatment	Benefit claimed
	24	Bland oil		7 improved by 50%, one with complete clearing of skin	
Reichert (1939) (109)	2 17½ & 20 yr.	Testosterone propionate	5 mg. 8 & 12 injections		Much amelioration
Riley (1939) (110)	12♀ 15–21 yr. 8♂ 17–21 yr.	Testosterone propionate Testosterone	Up to 50 mg. weekly av. dose of 300 mg. over 3 mo.	2 improved, 2 some improved, 4 not improved 5 improved, 1 not improved	"Slight but definite improvement as compared with controls do not suggest remarkable results."
	10♀ 13–23 yr. 2♂ 15 yr.	Distilled water		1 improved 2 some improved 3 not improved	

(109) reported great improvement in two cases treated with 5 mg. of testosterone propionate weekly. Control studies were not reported. Riley (110) obtained slight improvement in 20 cases treated with about 300 mg. of testosterone propionate distributed over a 3-month period. Cornbleet and Barnes (70) treated patients who had acne,

sex not stated, with injections of 10 mg. of testosterone propionate intramuscularly once weekly for 3 months or more. The condition of 24 patients was improved at least 50%. In 9 the eruption cleared entirely. Of these, 15 suffered a relapse from 2 weeks to 3 months after cessation of treatment. These 5 were given further injections of testosterone propionate, 3 again showed improvement while two cases received no benefit. Of 24 patients with acne who were given only sesame oil, the vehicle for testosterone propionate, 7 showed 50% improvement.

These results taken as a whole (table 4) are not impressive and do not indicate any great value in the treatment of the acne with testosterone propionate. The rationale is not bolstered by the fact that eunuchoid and castrated men who receive large doses of testosterone propionate for long periods of time may continue to exhibit acneform eruptions. It is true, however, that with continuation of treatment, the response may diminish and it is not altogether impossible that there may be somewhat of a parallel between this and the course of acne in the adolescent. This analogy is further borne out by the repeated exacerbations occurring in the same individual upon a series of courses of androgenic therapy.

As therapy for acne, testosterone might afford some slight improvement in some cases, but is hardly warranted in view of the expense and possibly dangerous nature of this treatment. In view of the present scarcity of data regarding the influence of exogenous male hormone on the adolescent, long-continued administration of androgens is not commendable, especially in girls.

B. Treatment with estrogenic and gonadotropic (luteinizing) substances. (table 4). The use of estrogens, which might be expected by some on theoretical grounds (antagonism between androgens and estrogens) to negate the seborrheic action of androgens, has not been attended as yet by any measure of definite success. It would seem that the quantity and nature of hormone and the duration of trial employed in several instances might not have provided a satisfactory test. Claims have been made, but there is no clear or acceptable proof that gonadotropic (luteinizing) substances are of value in the treatment of acne. The use of potent estrogenic and gonadotropic substances, especially for extended periods, must also withstand criticism for undesirable and dangerous side effects. Moreover, all such treatment is on empirical grounds and its true analysis awaits knowledge of the pathogenesis of acne.

SUMMARY

Eunuchoid individuals, who did not mature sexually, never had acne.

Upon administration of male hormone substance, testosterone propionate, to eunuchoid and castrate men, to prepubertal boys and to ovariectomized women, some of these individuals developed comedones, papules and pustules. When the treatment with hormone was terminated, the acneform responses diminished and began to disappear. Additional courses of medication given to these patients at later dates were accompanied by similar conditions with subsequent disappearance of the lesions during intervals between treatment with testosterone compounds. A close relationship of this acne to male hormone substance is attested by the rapidity with which the lesions fade upon cessation of androgenic therapy and by the fact that a developing papule which has undergone retrogression will again become inflamed if treatment is soon resumed.

In appearance the lesions are like those found at puberty. These and other considerations emphasize the interpretation that stimulation of sebaceous secretions and possibly some degree of acne of adolescence are not due to "deranged metabolism" or "endocrine dyscrasia" but to sequelae of sexual maturation.

Susceptible individuals do not develop acne unless adequate gonadal hormone substance is present. Presumably factors of an infectious, congenital or dietary nature exist prior to administration of hormone but are in themselves ineffective in the absence of at least a certain degree of body stimulation by androgens (or possibly by other agents stimulating the pilosebaceous structures).

Acne occurred in most but not all patients receiving adequate doses of hormone. Differential susceptibility in the present series does not appear to be determined by color of hair or skin or by the previous occurrence of puberty; men who pass through puberty before orchidectomy may or may not exhibit acne upon treatment. The greatest severity of eruptions was observed in a man with a history of severe acne as an adolescent.

The severity of the eruptions varied with the time elapsed since stimulation of the sebaceous glands and with the duration and continuous nature of androgenic therapy. The latent period between the administration of androgen and the appearance of acne, and to a much lesser extent the persistence of acne after the cessation of therapy, indicate a lag in this system.

Male hormone substance may be involved in various clinical conditions accompanied by acne, such as in puberty, adrenal virilism and arrhenoblastomata.

It is suggested that the stimulation of sebaceous secretions and the adjustment between follicular secretion and excretion are primary factors in production of acneform lesions. The positive relationship of male hormone substance to the stimulation of sebaceous secretions acquires added significance in view of the correlation of seborrhea with acne and

with infection of the pilosebaceous apparatus. Sexual hormones may also, perhaps, bear a relation to furuncular folliculitis in adolescence.

The fact that male hormone substance may induce acne in susceptible individuals is not proof that the sole cause of acne is the action of male hormone substance. Other factors and an "innate predisposition to acne" (as evidenced by identical twins) are undoubtedly of great importance.

Androgenic substances stimulate sebaceous secretions in various parts of the body not subject to acne, such as in the preputial gland.

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THE TREATMENT OF A CASE OF IMPOTENCE WITH A COMBINATION OF PITUITARY GONADOTROPIN AND TESTOSTERONE

NON-HYPOGONADAL IMPOTENCE

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THE TREATMENT of non-hypogonadal impotence in the male with testosterone has given inconsistent results. Success has been reported by Miller, Hubert and Hamilton (1) and Thomas and Hill (2) while failure has been noted by Rennie, Vest and Howard (3) and Pool, Cook and Kepler (4). Carmichael, Noonan and Kenyon (5) observed relief from impotence in seven of eighteen patients but concluded it was probably due to psychological factors. Psychological bias does not seem to explain the difference in achievement because in all groups bland solutions were used as control material. The possibility is presented, therefore, that in some instances it may be necessary to supplement the gonadal material with other hormones before the dysfunction can be corrected. In the case herein reported success was reached by the use of a combination of pituitary and gonadal hormones.

A white mechanic of 45 complained of inability during the past year to have erections. No difficulty in this regard had been experienced previously in a married life of 25 years. Physical examination showed no evidence of abnormality except for moderate obesity. A basal metabolic rate determination showed a value of -12%. Psychogenic factors which might account for the impotence could not be discovered.

The patient's gonadal equipment was perfectly normal. There had been one child, born 2 years after he was married. The absence of other offspring was more from choice, apparently, than from any biological difficulty. Previous to marriage he had been sexually quite active. No seminal studies were made.

As a preliminary treatment he was put for a three months' period on desiccated thyroid, U.S.P., one grain daily; this relieved his fatigue but had no effect in the sexual sphere. Following this the administration of gonadal material was discussed with the patient. It was stressed that the injections would be at no cost to him, that the procedure was purely experimental and that undue optimism was unwarranted.

With this purposefully defeatist attitude the treatment was started. He was given testosterone propionate,[1] 25 mg. 3 times a week, intramuscularly for 6 weeks. No change whatsoever was noted. The medication was continued but to it was added 1 ampule (25 hypophysectomized rat units) of anterior pituitary gonadatropin[2] 3 times a week intramuscularly. Morning erections were noted after 10 days of combined treatment. Potentia increased to a fairly satisfactory level in 3 more weeks so that intercourse could be accomplished. This level of moderate improvement was held throughout another month of medication. He was then given a more concentrated preparation of anterior pituitary material, one ampule containing 100 U, 3 times a week. After 4 injections, erections reached a normal degree of function for 2 weeks. Subsequently, however, despite a continuance of medication, the improvement lessened and in 2 weeks subsided altogether.

It was considered that this cessation of effect might have been due to the production of an anti-hormone factor so all medication was discontinued.

After an interval of one month anterior pituitary medication was resumed on a dosage of 100 U 3 times a week. No effects were noted after 2 weeks and, as previously, improvement had been observed within the second week, it was felt that the gonadotropic material by itself was of no avail. Accordingly, testosterone was again added in a dosage of 25 mg. 3 times a week. A definite effect was again noted after

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[1] Testosterone propionate, in the form of Oreton, was supplied by the Schering Corporation, Bloomfield, N. J.

[2] The anterior pituitary gonadotropin was supplied by the Winthrop Chemical Co., Inc., New York City.

3 injections and reached a satisfactory level in another week. The combination of medications was continued for a total of 6 weeks with continued excellent results. At the end of this time it was discontinued and there resulted a gradual diminution in potency but intercourse could still be satisfactorily accomplished at the end of three months.

Androgen assays were made throughout the study (table 1).[3] Before the first administration of testosterone, the average of three 24-hour assays was 168 Oesting units which was within the normal limits as obtained in our laboratory. Subsequent assays showed no significant variation with testosterone alone and only a slight increase with anterior pituitary alone or in combination with testosterone.

Whether the success obtained in this case is due entirely to hormonal or psychological factors or possibly to both is the question at issue. The psychological factors do not seem to be the predominant ones in the present instance for three reasons. In the first place, the atmosphere throughout was one of extreme skepticism. Second, it would have been quite unlikely that an unsophisticated subject would have selected only the periods in which the two medicaments were given for the reporting of good results. It is unfortunate, however, that this possibility was not controlled by administering a bland solution with either of the hormones when given singly. Third, and this is most important, the diminution in effect of the first combination after its initial success would be unlikely to occur were the results primarily psychological.

Assuming that the restoration of potency was due solely to the hormonal material, the reason for its success is still obscure. Since testosterone does depress the pituitary, additional gonadatropin may be necessary as a corrective factor in the non-hypogonad individual before good results can be obtained. In this respect it is of interest to note that Miller, Hubert and Hamilton (1) got the most satisfactory effects with testosterone in castrates, less satisfactory results in hypogonadal subjects and the smallest increment of success in the psychogenically impotent cases. One might speculate concerning the varying degree of pituitary activity in the three types of cases and what influence it might have upon the results obtained.

TABLE 1

Medication	Androgen Output per 24 Hours U	
	10/ 2/39	193—180
	10/ 4/39	166—160
	10/ 6/39	153—150
10/9/39 Testosterone, at 25 mg. t.i.week, begun		
	10/10/39	220—220
	10/17/39	173—165
	10/26/39	100—108— 96
	11/ 7/39	206—195
	11/14/39	136—143— 150
	11/21/39	165—152
11/24/39 Testosterone discontinued.		
12/4/39 Testosterone (25 mg.) plus Ant. Pit. (25 U) t.i.week, begun		
	12/ 5/39	193—175
	12/26/39	220—200—180
	1/24/40	186—160
1/31/40 Ant. Pit. increased to 100 U t.i.week		
	2/28/40	155—165
3/1/40 All medication discontinued.		
	3/21/40	300—269
	4/ 3/40	227—225
4/4/40 Ant. Pit. (100 U t.i.week) begun		
4/18/40 Ant. Pit. (100 U) plus testosterone (25 mg.) t.i.week		
	5/16/40	275—278—270
5/29/40 All medication discontinued.		

SUMMARY

A 45-year-old healthy male with impotence of 1 year's duration was treated with a series of intramuscular injections of testosterone (75 mg. weekly) and anterior pituitary gonadotropin (300 U weekly). Each medication singly had no effect upon the impotence. Success was achieved only when the combination of medicaments was administered.

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[3] The androgen assays were carried out by Dr. J. M. Looney, using his modification of the standard Oesting technic. The procedure in his hands has indicated that one Oesting unit equals 0.1 mg. of androsterone in the range between 2 and 5 U of the Oesting colorimeter. Consequently the value of 168 U represents 16.8 mg. of androsterone.

HYPERINSULINISM

SPONTANEOUS AND ARTIFICIAL HYPERINSULINISM

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A BUSINESS MAN 47 years of age was admitted to the Polyclinic Hospital, July 25, 1940, on the service of Dr. John Carroll, to whom thanks are due for the privilege of making the following observations.

The family and personal history were non-contributory except for an automobile accident 8 years ago. Physically he suffered only a severe shaking up, but his mother was injured and he believed her dying, so that he was under extreme emotional distress with the thought of having caused his mother's death. Having always been well before, he had the definite opinion that this accident was the origin of his illness. It was only after 6 months, however, that he began to have mild attacks of general twitching about once a month. Three years later he went into a coma lasting 7 or 8 hours. The spasmodic attacks increased in frequency and severity, but were limited chiefly to the lower part of the body and he never again lost consciousness. Two years ago he went to a hospital where hypoglycemia was diagnosed and a high carbohydrate diet prescribed, especially in the form of frequent fruit drinks heavily sweetened with sugar. His attacks were thus for the most part prevented but still occurred at times; he had gained some forty pounds of weight and was becoming progressively more obese, and he sought treatment for these reasons.

Nothing abnormal was found in ordinary examinations or in x-rays of the pituitary region, which were studied especially because of the traumatic history. Attacks were brought on by withholding food or by exercise, and were prevented or cured by carbohydrate. Consciousness was retained but there were general tremors and marked loss of control and spasms of the legs. Thus the patient might feel an attack coming on, start from his chair to get a glass of fruit juice across the room, and be found on the floor helpless with convulsive jerking of his legs, but apologizing for his condition and explaining that he would be all right as soon as he could get a little sugar.

Attempts to ascertain the definite blood sugar levels before, during and after attacks were not executed very well. Analyses at various symptom-free times during the day and night, before and after meals, all ranging between 29 and 43 mg. %, sufficed to demonstrate a persistently low blood sugar and also a tolerance of hypoglycemia such as other authors have noticed. The margin determining the onset of symptoms may have been narrow, for on one occasion a blood sample taken in the beginning of an attack contained 25 mg.% sugar, while another sample taken shortly after the attack had been relieved by fruit juice, contained 29 mg.%. A glucose tolerance curve was not made, but epinephrine was tested with the usual 1:1000 solution as follows. At the first hour ¼ cc. was injected subcutaneously, at the second hour ½ cc., and at the third hour 1 cc. Blood sugars taken from the first to the fifth hours were 47, 41, 59, 40 and 51 mg.%.

These facts seemed sufficient for a diagnosis of hyperinsulinism, as against other forms of spontaneous hypoglycemia. Control was attempted with diets of 70 gm. carbohydrate, 120 to 150 gm. protein and 1300 total calories. Attacks were numerous in spite of a subdivision of this diet into six feedings. A change was then made to 200 gm. carbohydrate, 60 gm. protein and 1300 calories. Attacks ceased except for one in the morning before breakfast. Therefore, because the final meal at bedtime did not assure complete safety until the next breakfast, an extra lunch of 25 gm. carbohydrate was added at 3 A.M. The patient was discharged with this schedule on August 14. The blood sugar before breakfast on that day was 74 mg.%; i.e., higher than had been found on his original regime of extremely high carbohydrate.

In the hospital the patient's weight diminished from 237 to 228 lb. On returning home he imitated the hospital diet without weighing it, and was allowed to increase the protein within comfortable limits. His only inconvenience was in eating six times daily and waking with an alarm clock to take the seventh lunch at 3 A.M. At last report he was free from all attacks, feeling and working better than for several years, and continuing to lose weight.

DISCUSSION

It is possible to omit most references to clinical literature because of the excellent reviews by Harris (1), Wilder (2), Conn (3) and others. There is still a need for correlation with experimental facts which other writers have omitted. Part of this information is derived from experiments which had to be broken off twenty or more years ago, and the attempts to continue them have been limited and frustrated. Some vague clinical conceptions may be clarified in the light of experimental findings.

The great majority of clinical cases of hyperinsulinism are mild, especially in their early stages. Just as an injection of only a few units of insulin in a normal person between meals will often cause hypoglycemic symptoms, so also the symptoms in spontaneous cases may be due to an unregulated insulin production such as might be expected, for example, from a tumor. For this condition the clinical litera-

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ture already supplies the name dysinsulinism, indicating a disorderly rather than an excessive insulin production. Nevertheless, in the well marked cases of hyperinsulinism there is a prevalent impression that a large excess of insulin is present. Sometimes there is an inference concerning remarkable activity of the cells in a tumor, which perhaps is only of pea size and yet supposedly floods the body with so much insulin. The experimental evidence that the insulin surplus is usually small is as follows.

(*A*) Epinephrine or sometimes even ephedrine prevents the attacks in ordinary cases of spontaneous hyperinsulinism. But it may be questioned if epinephrine is a true or specific antagonist to insulin. It happens to be able to antidote small doses of insulin through its incidental action of discharging glucose from liver glycogen when a considerable glycogen supply is present. But in animals receiving large doses of insulin, and particularly when the doses of both insulin and epinephrine are repeated, the antidoting power is found to be trivial or absent (4). For example, in rats very large doses of insulin can be temporarily antidoted by 0.2 gm. of glucose. The question can thus be posed: does the largest possible dose of epinephrine possess antidotal power equivalent to 0.2 gm. of glucose? A very emphatic negative answer is obtained. The antidoting by epinephrine is therefore incompatible with the idea of a large and prolonged excess of insulin secretion.

(*B*) Successful treatment with diets comparatively low in carbohydrate has been described (1, 5, 6) and more recently Conn (3) has strongly advocated a high protein diet. This diet, containing 50 to 75 gm. of carbohydrate and 120 to 140 gm. of protein, is not strikingly high in either protein or total glucose values; but the more gradual and prolonged release of glucose from protein (7) than from preformed carbohydrate furnishes a theoretical basis for the excellent clinical results reported with this method in suitable cases. There is a lack of the most instructive basis which might be furnished for a diet treatment, namely tests of the quantity of injected insulin against which the given diet will protect. Observations in human diabetes and animal experiments with injected insulin prove that protein actually protects against appreciable quantities of insulin. The animal experiments also prove that the degree of this protection is small. The low total glucose value of the Conn diet has been mentioned, and actually no human being can eat enough protein to protect against a very large excess of insulin. Carbohydrate offers a far more abundant and more effective source of glucose for animals injected with insulin. Likewise the case described in this paper was too severe to be controlled with protein and required higher carbohydrate. Therefore the Conn diet is a proof of the mild degree of insulin excess in the numerous cases successfully controlled by it.

(*C*) Another class of cases, particularly those associated with pancreatic island tumors, are reputed to be too severe to be amenable to diet. They have often been treated with glucose amounting to hundreds of grams daily, and sometimes were supposed to require continuous glucose infusions. Animal experiments confirm the view that insulin accelerates the consumption of both glucose and glycogen, partly by combustion but chiefly by conversion into fat or unknown forms. Also large insulin doses accelerate this process more strongly than small doses, and hence demand more carbohydrate as an antidote. Mainly, however, the widely prevalent impressions on this point are false. One such impression is that the effect must be proportionate to the insulin dose. The actual law is that increases of insulin dosage increase the duration much more than the intensity of action (4, 8, 9). A rat receiving 1000 U of insulin does not require much more glucose per hour than a rat receiving 10 or 20 U, but the duration of the effect is vastly greater with the larger dose. The second prevalent misconception is that the quantity of glucose required for antidoting must be proportionate to the quantity of insulin. Actually, no direct reaction between glucose and insulin in the body has ever been found. In particular, the conception of an interaction whereby insulin and glucose are mutually destroyed in some quantitative relation is wholly imaginary. An empirical rule that one unit of insulin may be antidoted by one gram or any other quantity of glucose can be only accidentally true for some prevailing set of conditions, and is subject to extreme changes with different physiological and pathological states, different sizes of dose and many other variables. In fact the entire conception of an antidote is misleading, inasmuch as glucose does not directly counteract the insulin but merely replenishes the blood sugar. A striking example is the 'antidoting' of 1000 U of insulin by 0.2 gm. of glucose in a rat (4); but in larger animals, including man, 10 to 20 gm. of glucose may be required for this same dose of insulin. Also, no amount of insulin can accelerate the reduction of blood sugar beyond a certain maximum rate; therefore, regardless of the insulin dose, it can be 'antidoted' by the above-mentioned quantities of glucose administered at intervals of perhaps 1½ or 2 hours throughout the duration of insulin action. The absence of a quantitative relationship is further illustrated by the fact that the largest possible doses of glucose do not cause insulin to be used up in the body any more rapidly than with the above-mentioned minimal doses.

In clinical tests, the above rules were found to hold true when a diabetic who required less than 100 U of insulin per day was given experimentally 750 or 1000

u in single injections (4). It is reasonably certain that neither island cell cancers nor any other clinical conditions ordinarily represent an excess production of anything like 1000 u of insulin per day. Apparently, therefore, either the enormous or continuous administrations of glucose are unnecessary, or else some disturbance is present besides simple hyperinsulinism. In the treatment of spontaneous hypoglycemia, the mistaken theories mentioned above have entailed two possible consequences. First, as is plainly seen in animal experiments, huge and prolonged glucose administration can produce a state of prostration and convulsions which may be confused superficially with the effects of insulin. Second, as is emphasized by all recent clinical writers, excessive quantities of glucose stimulate the island cells to an overproduction of insulin. Hence an exaggerated discharge of insulin, such as never occurs ordinarily, may possibly be induced in a brief terminal period directly by the treatment.

(*D*) Any remaining argument that some types of cases may represent actually large and prolonged excesses of insulin production can be settled by reference to the specific toxicity of insulin. This toxicity, which is independent of glucose administration or blood sugar levels, is demonstrable with sufficiently enormous single doses of insulin in any of the common laboratory animals (4). It is demonstrable also in the form of a chronic intoxication when comparatively small doses of insulin are continued daily for a number of weeks or months. There are wider individual variations of insulin sensitiveness in man than in any species of experimental animals. Though some normal persons are distressed by doses of only a few units, the use of insulin for fattening in tuberculosis and other conditions (10) shows that even the most tolerant individuals develop symptoms from too long continuance of moderate doses. For example, nondiabetics who at first thrive on 50 to 75 u of insulin per day commonly begin to react unfavorably after variable periods of weeks or months (11). Therefore, if a patient with spontaneous hyperinsulinism exhibits symptoms of nausea, prostration and perhaps convulsions, leading to death within a few days regardless of glucose administration or blood sugar levels, the condition might conceivably be due to overproduction of insulin to the extent of several thousand units daily. If a patient during several weeks or months exhibits progressive anorexia, weakness and emaciation not influenced by glucose or other treatment, he may possibly be suffering from an overproduction of perhaps 50 to 100 u of insulin per day. Inasmuch as such syndromes are rare, or exist only as terminal states usually in the presence of complicating factors, the entire evidence is seen to support one conclusion; namely, that the great majority of cases of spontaneous hypoglycemia due to insulin represent either dysinsulinism or very mild degrees of overproduction of insulin.

DIFFERENT FORMS OF INSULIN

Not only the foregoing deductions concerning hyperinsulinism but practically all existing physiological and clinical knowledge of insulin have been derived from experiences with injections in animals and human beings. Therefore a searching inquiry is proper into the validity of this method for establishing objection-free conclusions. One possible objection or doubt may be found in the lack of certainty as to whether or not the injected insulin is strictly identical with the substance discharged from the pancreatic island cells.

The strongest suggestion of such a doubt is contained in the observations of Campbell (12), who witnessed the development of insulin from the time of its discovery. The records of his patients showed that the effect of the earlier and cruder preparations was far longer lasting than that of the latest highly purified product. It is known that the absorption of injected insulin may be modified by reaction or by substances present as impurities. On the other hand the secretory granules of the beta cells evidently do not consist of the insulin of commerce. There is no proof that the finished secretion discharged from these cells consists of a solution of crystallizable insulin. On the contrary, competent students admit the possibility or even probability that insulin leaves the island cells as a compound, perhaps with protein. Such a hypothetical compound may conceivably be broken down by precipitation and extraction processes into a series of simpler substances, until with the most drastic purification a highly active but artificial crystalloid may result. One corollary of this hypothesis is that the natural island secretion may differ from the artificial extract in respect to rapidity of action and perhaps other properties, and the slow action of crude extracts observed by Campbell may be explained as due to intermediary products which retain some resemblance to the natural substance.

If it be true that the insulin normally discharged by the pancreas is combined in a large molecule, a prolonged action of this compound must represent a slowness in metabolism rather than a slowness of absorption. The only comparison possible, however, is with a compound which has a prolonged action due to slow absorption, namely protamine insulin. Any differences in potency between regular and protamine insulin in diabetic treatment are trivial in comparison with the differences found in tests in normal animals (4). For example in a rat, the total amount of glucose required to protect against 10 u of protamine insulin is a large multiple of the amount required to protect against 10 u of regular insulin, merely because the

prolonged action of the protamine insulin requires so many more glucose injections. Apparently, therefore, a secretion of insulin in the form of a compound with prolonged action might be a means of great economy in insulin production. Under this hypothesis all estimates of the daily insulin production or insulin requirement of man or animals are fallacious, because a basis of comparison with artificial insulin is lacking. Also on this assumption the belief of authors that they imitate the natural secretion of insulin by intravenous injections is mistaken, because they are injecting a foreign substance. The rapid destruction of insulin after sudden intravenous injection of large amounts, the greater potency of the same dose when injected subcutaneously, and the great gain in potency as a given quantity is fractionated into more and more numerous interval doses, might all be harmonious with the hypothesis that small amounts of insulin can form at least some kind of makeshift combination when in contact with tissues, but that a large uncombined portion, especially with large doses, is wasted.

Such speculations are related to the present topic in two ways. First, if they are correct the attempt to make close comparisons between spontaneous hypoglycemia and injections of commercial insulin breaks down. Second, existing observations suggest that normal animals and human beings cannot tolerate even moderate insulin dosage for many months continuously without developing symptoms which are largely or wholly absent in cases of spontaneous hyperinsulinism. If this suggestion can be confirmed by positive experiments, the result together with Campbell's experiences would constitute two-fold evidence in favor of the secretion of insulin in the form of a compound different from the prepared extract.

To these two points may be added a third, in the form of an analogy. Physicians and investigators commonly assume that the protamine compound of insulin is merely a means of obtaining a delay of absorption, and that regular insulin is split off at some point so as to have the identical effect. It would then be natural for investigators to administer protamine insulin as a convenient means of imitating spontaneous hyperinsulinism. The incorrectness of these ideas is illustrated by three classes of evidence, of which the first two are only suggestive but the third appears positive.

(*a*) It is known that the reaction symptoms from overdoses of regular or protamine insulin in the same patient are often different, and there is no definite proof that this difference is due merely to a different rate of fall of blood sugar.

(*b*) MacKay, Callaway and Barnes (13) were able to fatten rats with protamine zinc insulin to a degree which has never been equalled with regular insulin. Apparently the breed of rats or some details of diet or method are important, because the results of these authors are beyond question, but I was unable to duplicate them using several strains and colors of rats, because of fatalities; i.e., daily doses of 6 to 12 U of protamine zinc insulin become cumulative and toxic. On the other hand, equal doses of regular insulin, on account of the extremely high insulin tolerance of the rat, have effects which are trivial in degree and duration. Freyberg (14) set his small experience against a mass of positive laboratory and clinical proofs, when he attempted to conclude that the increase of appetite and weight with regular insulin is negligible or "psychic." His failure is explainable by faulty individualization of treatment, the use generally of too small doses, and the probability that his small series included several of the well known refractory type of cases. When rats on a suitably concentrated diet, such as bread soaked in milk, receive regular insulin in doses sufficient to produce an appreciable degree and duration of effect, such as 20 or 30 U two or three times a day, their increase of appetite is sufficient to convince any investigator and gains of 20 to 40 gm. in weight are easily obtained. Suitable doses also cause marked hunger and brief gains of weight in rabbits on oats and other high-carbohydrate foods. MacKay and coworkers did not mention the effect of larger doses of protamine insulin, or any periods longer than 20 days, therefore, the fattening obtained may have been temporary, as it is with regular insulin. A strict comparison of the two kinds of insulin is laborious, because it would require that small doses, such as used by these authors, be fractionated into small injections given every hour or two in order to imitate the slow absorption of protamine insulin, and this day and night program should be continued for one or two weeks. I approximated these conditions to the extent of injections every 4 or 6 hours in a few experiments lasting 7 to 10 days, which confirmed the increase of potency which is known to occur as insulin is divided into larger and larger numbers of interval doses. The gains in appetite and weight were less than those reported by MacKay, Callaway and Barnes. Accordingly, a qualitative difference between regular and protamine insulin is possible but not proved.

(*c*) A positive difference of this kind appears to be established by a previously published experience (4), which may be summarized as follows. A single subcutaneous injection of 10 or 15 U of protamine zinc insulin in a rat produces effects for 3 days or more, which is longer than the effect of 500 or 1000 U of regular insulin. The absorption of regular insulin is rapid, whereas the amount of protamine insulin absorbed per hour is obviously very small. Nevertheless a strong rat can survive 500 or 1000 U of regular insulin, while 50 or 60 U of protamine zinc insulin is inevitably fatal. Furthermore the appetite is increased

by moderate doses and reduced by the largest doses of regular insulin, but nevertheless the rat ordinarily remains willing to eat enough bread or glucose to preserve life. But with doses above 20 U of protamine zinc insulin the appetite is fickle, and with more than 50 U there is early and absolute anorexia. This difference in toxicity, which defies explanation on any quantitative basis, seems to prove a qualitative difference, in other words that protamine zinc insulin enters into metabolism as a distinct compound and is not merely split to yield regular insulin.

Zinc has been proved to be non-toxic in the quantities used. If we inquire whether the toxicity could be due to protamine split off from the insulin, there are three grounds for an answer.

First, using protamine kindly furnished by Dr. M. Sahyun, several experiments on rats and rabbits were performed using intravenous or subcutaneous injections of protamine alone, also simultaneous injections of protamine in one part of the body and insulin in another part. These experiments were not completed to the desired accuracy, but they left the impression that while protamine has toxicity, the quantitative relations and the symptoms both differ from those of protamine zinc insulin.

Second, comparative injections of regular and protamine zinc insulin seemed to offer a better means of answering the question. The toxic symptoms of protamine insulin can be produced by a trivial quantity, because the anorexia may develop within an hour after the subcutaneous injection. Also the toxicity of protamine alone is manifest with intravenous injections. Intravenously, with graded doses and especially with large doses of the two kinds of insulin, unmistakable differences are found, in that the protamine zinc insulin has a more prolonged effect and is more toxic than regular insulin. But these differences are far less than with subcutaneous injections. In being fairly rapidly destroyed after intravenous injection, also less potent and less toxic than with subcutaneous injection, protamine insulin obeys the characteristic laws of an insulin and not of a protamine. This, therefore, is a second reason for concluding that protamine zinc insulin enters into metabolism as a compound form of insulin and not as insulin and protamine separately.

Third, evidence was obtained (in rabbits and cats) that injections of anterior pituitary emulsion prepared according to the Young method have a similar influence in counteracting both the toxicity of ordinary insulin and the higher toxicity of protamine zinc insulin (15). These experiments, though not completed, nevertheless reached a stage which seemed to furnish final proof that the observed toxicity is due to the insulin compound and not to protamine split off from it.

The fact is now familiar concerning several endocrine organs, that either compounds of the hormone or substance chemically related to the hormone may produce similar or only slightly different effects. Although the proof is not absolute, the weight of evidence seems to favor this view for insulin; so that the physician who uses regular or protamine insulin is actually treating diabetes with two distinct substances, and there is the further theoretical possibility that neither of these is identical with the secretion of the pancreatic islands. The toxicity of protamine insulin is too slight to be of any significance therapeutically, except that regular insulin is safer if there is ever a question of very large doses in non-diabetics, for example in the insane. Inasmuch as both kinds of insulin are so satisfactory for diabetic treatment, there is reason to believe that the artificial hyperinsulinism produced by either of them will bear a close general resemblance to spontaneous hyperinsulinism, but account must also be taken of possible differences in detail between the artificial and natural conditions and between the effects of the two insulin preparations. In late years a number of other insulin compounds have been prepared with a view to delayed action, and there would be interest in tests to as certain whether these enter into metabolism as distinct substances with perhaps perceptible differences in effect. The most important opportunity along this line has not yet been utilized by chemists; namely, if it is true that insulin can enter into metabolism in a compound form, producing its characteristic effects in the utilization of carbohydrate, an opportunity is afforded for linking insulin with some substance which can be traced through the body, thus furnishing new information on the distribution and function of insulin.

TREATMENT OF HYPERINSULINISM

Clinical and experimental information may be correlated in regard to dietary management, treatment of emergencies and cure.

Dietary management. (*a*) *Protein.* The liberal protein allowances recommended by Conn may be considered advantageous both in cases which are controlled thereby and in the more severe cases which require reinforcement with carbohydrate.

(*b*) *Carbohydrate.* Authorities now agree that stimulation of insulin production by excessive carbohydrate should be avoided. Ordinarily there is no need for an excess, because successful control depends less on the aggregate amount than on the proper spacing of fractional feedings. It is questionable if either epinephrine or ephedrine is as convenient and agreeable to most patients as the eating of a little carbohydrate between meals.

(*c*) *Fat.* A maintenance diet which is low in carbo-

hydrate is necessarily high in fat, and in this respect the dietary plans of Waters (5), Shepardson (6), Harris (1), Conn (3) and others agree. Best and collaborators (16) have furnished direct experimental proof for the belief that fat, at least during short periods of administration, does not call for any insulin production, In diabetic patients ketosis is known to be accompanied by enormous increases of the insulin requirement. There appear to have been no studies of insulin production or insulin tolerance in ketosis produced artificially in normal animals. Withdrawal of carbohydrate and increase of fat to the extent of causing ketosis is not feasible in spontaneous hyperinsulinism, because attacks occur when the carbohydrate falls too low.

(*d*) *Total calories.* When carbohydrate is kept fairly low, changes in the fat allowance essentially determine the body weight. Harris and others have clearly understood that a patient able to digest food need not be either too fat or too thin because of hyperinsulinism. The demands of hypoglycemia can be supplied by small frequent carbohydrate feedings. A ravenous appetite can be satisfied with bulky low-calory foods. An emaciated patient can be built up with liberal allowances of fat.

(*e*) *Body weight.* Obesity predisposes to diabetes, and the insulin requirement of diabetics can be raised by gain of weight or lowered by loss of weight to far greater degrees than by any changes in the mere carbohydrate allowance. There seems to be no proof whether anything similar occurs in hyperinsulinism; for example, whether obesity will help the patient to consume his excess insulin; whether it will tend to depress the function of his pancreatic islands, or whether on the contrary it will stimulate insulin production. The single patient described in this paper appeared to be better off in general when his excessive weight was reduced, and his need for carbohydrate was at least not elevated thereby. Larger numbers of clinical observations are needed to decide this point.

The principal outstanding question pertains to the ultimate outcome; whether (in non-neoplasmic cases) an optimum diet will enable the patient to remain stationary or improve, or whether changes for the worse are inevitable. There is reason to suspect that aggravation has sometimes heretofore been induced by wrong diet. The establishment of a fairly stationary condition will permit of more accurate evaluation of the use of insulin (17) or any other proposals for diminishing the insulin production.

Treatment of emergencies. (*a*) *Artificial hyperinsulinism.* For illustration, we may think of the serious condition that would be created if a would-be suicide should inject himself with 200 cc. or more of U-100 insulin, or the much more dangerous state that would result from an equivalent dose of protamine zinc insulin. Judging from animal experiments, the severe hypoglycemic tendency in the former case would continue for several days, and in the latter case for a week or more. Instead of panicky and harmful attempts to neutralize with correspondingly large carbohydrate administration, there should be a realization that any beginning hypoglycemic attack, regardless of the amount of insulin, can be overcome by giving carbohydrate by mouth or glucose by vein in the moderate quantity required to replenish the blood sugar, perhaps 10 to 30 gm. Carbohydrate by mouth is harmless, but probably could not be taken, if we judge by the nausea produced in most species of animals by extremely large insulin doses. Glucose injections are therefore necessary, but are toxic if too large and long continued. There are only two possible causes of death. One of them is glucose intoxication. There is as yet no information whether this represents a chemical effect of glucose, which might be overcome by vitamins, amino acids or other physiological aids, or whether it is due merely to osmotic or other physical injury. The only known way of avoiding this danger is to keep the administration of glucose down to the minimum that is effective. It is only necessary in this moderate manner to control each incipient hypoglycemic attack, in order to 'antidote' insulin up the maximum limit and to see the attacks finally cease.

Beyond a certain maximum limit, insulin has a specific toxic action, manifested in prostration, convulsions and death, which can be delayed but not prevented by glucose. Epinephrine and all other drugs are useless. Also attempts to retard absorption by means of a tourniquet, if the insulin was injected in a limb, are ineffectual. Although protamine zinc insulin is so much more toxic than regular insulin, a successful method of treatment is shown by the animal experiments (18), inasmuch as excision of the area of injection accomplishes a spectacular cure, which is not possible in the case of ordinary insulin. In a sufficiently desperate intoxication with either kind of insulin, as long as a potent purified pituitary extract is unavailable, it appears feasible to prepare a fresh anterior pituitary emulsion by the Young method and inject it in considerable amounts. The crisis is likely to be ended by either recovery or death before the danger of allergy from the foreign protein arises. The anterior pituitary substance is not a complete and immediate antidote for the insulin, because glucose is still needed, but the amount and the duration of glucose administration are reduced. Also, although the specific toxicity of insulin is associated with functional and organic damage in the central nervous system, this toxicity seems to be greatly relieved by the pituitary material. In line with the discoveries of Long (19), there were indications in other unpub-

lished experiments that the adrenal cortex has a more or less similar antidotal power against large insulin doses, but the investigation along this line was not completed.

An incidental new deduction from these results is as follows. The specific toxic action of insulin upon the nervous system cannot be due to hypoglycemia in experiments in which hypoglycemia is prevented at all stages. Therefore the anterior pituitary principle appears to act antagonistically to insulin in other ways besides the regulation of blood sugar.

(*b*) *Spontaneous hyperinsulinism.* The treatment should presumably follow the lines indicated for the experimental condition, avoiding the use of glucose in such quantities as to cause either intoxication or stimulation of insulin secretion. Some deaths may possibly have resulted unnecessarily from these causes. If it is not possible to control the hypoglycemia by small glucose injections at intervals of one to two hours—in other words, if the disappearance of glucose is accelerated more than is possible with the largest imaginable insulin injections—a qualitative difference is evidently established between spontaneous hyperinsulinism and the effects of commercial insulin. Also if epinephrine has any but the most trivial and transitory effect, the condition is either milder than supposed or is different from artificial hyperinsulinism. Various authors have already expressed the desire for a purified anterior pituitary extract as a specific remedy, but in a sufficiently acute crisis it is theoretically justifiable to try temporary use of the crude emulsion as mentioned above.

Cure. Following the discovery of spontaneous hypoglycemia by Harris, the demonstration of hyperinsulinism and the first cure by removal of a pancreatic tumor were accomplished by Wilder. The subsequent surgical cures have been brilliant but few. In regard to the severe cases, for which diet and medical treatment are inadequate, the universal neglect of existing experimental information can be pointed out as follows.

Pancreatic resection in cases without discoverable island tumors has frequently been unsuccessful, and authors are divided concerning the advisability of the operative attempt. Experimentally, it is possible to bring about a selective destruction of islands, either partial or complete, without important permanent damage to the acinar tissue, by clamping the pancreatic vessels for periods of twenty minutes to two hours (20). These results in dogs can presumably be duplicated in the human subject, and this method has theoretical specificity for the cure of diffuse hyperplasia, adenoma, etc., of the islands. Practically, however, there are hindrances in the probable necessity of repeated laparotomies for several successive clampings, and the advisability of preliminary fasting (with glucose injections for hypoglycemia) as a precaution against fat necrosis, so that surgeons may usually continue to prefer resection.

The local asphyxia produced by temporary clamping has a considerable degree of specificity in killing tumors selectively in comparison with various normal tissues (21). In view of the foregoing experiments with normal islands, there is all the more reason to anticipate that neoplasmic islands may be selectively destroyed in this way. But though the method might be applied to metastases in the intestine and certain other organs, it could not be applied to the liver because of the sensitiveness of this organ to asphyxia. As the liver seems to be the first and commonest site of such metastases, the clamping method may be regarded only as an untried suggestion offering no advantages over the known results of resection.

Nevertheless, more effective treatment is evidently needed for the most dangerous cases of hyperinsulinism. As the most hopeless examples, we may select the cases of island cell malignancy with metastases in the liver or elsewhere. The published records give the impression that such growths often consist entirely of beta cells, not of alpha, duct or other cells. The staffs of institutions receiving such cases, though doubtless familiar with the endocrine influence upon sex-cell tumors, have never grasped the inviting opportunity for an endocrine attack upon beta-cell tumors. Combinations of any or all of the following procedures can be used according to need.

(*a*) The pancreas should be resected as far as seems desirable. A sufficient remnant should be left to provide for digestion, because of the difficulties created by a complete permanent absence of pancreatic juice.

(*b*) The remnant should be subjected to clamping of its blood vessels, if necessary by repeated laparotomies.

(*c*) The diet should be one of maximum carbohydrate and minimum fat, of the same general type which in the recent past was widely publicized for diabetic treatment, in order to contribute to the breakdown of islands as powerfully as possible. Usually this should be reinforced also with glucose injections.

(*d*) Lacking a purified diabetogenic hormone, injections of fresh crude anterior pituitary emulsion should be used freely. The beginnings of allergy should be countered by changing to glands from a different species—beef, sheep, horse, pig, etc. In this way the injections could probably be continued as long as necessary, for with the onset of severe persistent diabetes they would become unnecessary.

(*e*) These methods in animals suffice to destroy every beta cell in the body; and though it is uncertain whether malignant or normal cells would respond more strongly to this stimulation, there can be little

doubt that the complete result is feasible in patients. It is assumed that precautions would be taken against coma if necessary, and that a fairly long period of symptoms of severe diabetes would end in an emaciated state, from which the patient would be built up by insulin and treated as a 'total' diabetic throughout life.

(*f*) It may be ascertained by animal experiments whether the above conditions sensitize the island cells to irradiation (22). An increased sensitiveness under the heavy functional strain appears as a plausible theoretical possibility. In this event the preceding measures for destroying islands by hydropic degeneration could if necessary be supplemented by irradiation.

A case of beta cell cancer offering these therapeutic opportunities might well be welcomed by any investigator.

Relation to Diabetes

Fluctuations of tolerance are shown by the occasional appearances of lowered glucose tolerance or outright glycosuria in cases of hyperinsulinism. The most arresting phenomenon, however, is the rare transformation of diabetes into hyperinsulinism. An example is described by Joslin (23). These seem to be the only conditions under which anything like a cure of a severe long-standing diabetes has ever occurred. Assuming that it may be due to either an island tumor or hyperplasia of the islands, it furnishes the first proof of the important fact that human diabetes can be cured by some such process.

Second, the anterior pituitary is known to influence both functional and organic changes in the pancreas. A long-known accompaniment of acromegaly is visceromegaly, which includes hypertrophy of the pancreas. Young (24) found that with progressively increased injections of his anterior pituitary emulsion animals became increasingly resistant to it, and especially in rats increases of islands and of insulin content were demonstrated in the pancreas. Best and collaborators have added the brilliant demonstration that in dogs the degeneration of islands and accompanying diabetes produced by the Young extract can be prevented by insulin. Hypothetically, the full completion of such experiments might lead in normal animals to an artificial reproduction of 'spontaneous' hyperinsulinism, or in diabetic animals it might lead to a cure, provided that hydropic or other changes had not reached such a point that adequate restoration of beta cells was impossible.

Without reference to other work or suggestions along such lines, it is desired here only to summarize briefly two personal observations.

(*a*) Shortly after Young's first publication, I partially depancreatized a Scotch terrier so as to make a borderline condition with a liberal-sized remnant of about one-eighth of the pancreas, and then broke down the tolerance by carbohydrate diet and a few intraperitoneal injections of Young's extract. The animal was then kept on a weighed meat diet, with 3 injections of regular insulin every 24 hours, for 6 months until standardization was obtained on a quantity of meat which maintained constancy of weight and insulin requirement. Accuracy in such an experiment requires not only urine tests but also many ear-vein blood samples for micro analyses of blood sugar, because hyperglycemia without glycosuria can cause a gradual decline of tolerance which is plainly demonstrable and should be instructive for human treatment. Granting that the blood sugar is kept approximately normal, such an animal needs very careful watching because a hypoglycemic attack sometimes occurs unexpectedly by day or night and causes death more easily than in a human patient. The tolerance can be established precisely; for example in this dog the insulin requirement was 14 or 15 U per 24 hours, and without insulin 3 days of fasting reduced glycosuria to traces but left the blood sugar between 200 and 260 mg.

Thereafter during 4 months, intraperitoneal injections of the Young extract were given in variable ways; sometimes doses of 1 or 2 cc. once or twice daily, at other times doses from 1 to 5 cc. several days apart. The insulin requirement was thus doubled or tripled, and even with emergency insulin injections whenever needed a uniform control of the sugar was impossible.

The net result at the end of 4 months was a strictly unchanged condition. The insulin requirement was still 14 or 15 U daily, and 3 days of fasting affected the sugar in the same way as before. It could only be inferred that the treatment had produced no functional and probably also no organic change in the pancreas remnant. This result pertains only to an established and fairly severe diabetes created almost wholly by extensive pancreatectomy. It does not prejudice the results obtainable under other conditions, which may be much more promising.

(*b*) Some clinical observations were attempted in an altogether different direction, with the attention directed to the hypertrophy of the feet in acromegaly. Whether this represents a primary stimulus to circulation or to tissue nutrition, the condition seems strikingly opposite to the arteriosclerosis and atrophy in many diabetics. The observations were made from this viewpoint. One patient selected was an Italian man aged 62 years, with very mild diabetes easily controllable by diet without insulin, but with a tendency to slight stubborn hyperglycemia. He had claudication which prevented walking more than 4 blocks, but the circulation in the legs and feet was

sufficient to prevent atrophy or any apparent danger of gangrene. He was given an injection of 5 cc. of Antuitrin-G (Parke, Davis) once a week for 6 months, without positive result. Two elderly diabetic women, one with arteriosclerotic pains and the other with incipient dry gangrene, were given similar doses of anterior pituitary extract (Squibb) two or three times a week, for respectively 3 weeks and 2 months. No improvement resulted; the gangrene showed a possible slight change for the worse. The absence of effect upon the diabetes was to be expected, because it is known that the commercial anterior pituitary extracts are capable of producing insignificant transitory hyperglycemia but they do not contain the true diabetogenic principle. The acromegalic hypertrophies, however, are attributed to the growth hormone, which these extracts contain. I do not know of any reported case in which a patient with marked peripheral vascular disease developed acromegaly and the typical overgrowth of extremities. The apparent lack of stimulus to either nutrition or collateral circulation in the above experiments may represent an inability of the tissues or vessels to respond to the hormone. But it is scarcely reasonable to expect changes in the lower limbs unless the treatment is sufficient to produce symptoms or signs of acromegaly elsewhere. The dosage or the time was actually insufficient to produce appearances like acromegaly anywhere, and it is uncertain whether any more strenuous attempt should be made along this line to combat the present hopelessness of advanced peripheral vascular disease.

SUMMARY

A case of spontaneous hyperinsulinism is described, which was controllable without overnutrition and with considerable reduction in weight, but was not controllable without liberal carbohydrate.

A comparison is made with experimental artificial hyperinsulinism, with reference to general principles of treatment and also to proved or hypothetical differences between ordinary commercial insulin, protamine zinc insulin, and the natural secretion of the pancreatic islands.

Suggestions are made for a more radical specific treatment of the most dangerous cases of hyperinsulinism, including beta cell cancers, through various methods of producing hydropic degeneration of beta cells.

The proved effects of anterior pituitary extract upon the pancreas and diabetes invite further experimentation. Lack of success is reported in one attempt to relieve an established diabetes in a dog, and in slight attempts to influence arteriosclerotic conditions in human diabetes.

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LACK OF PERIMETRIC EVIDENCE FOR PITUITARY HYPERTROPHY IN DIABETES[1]

DIABETES

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BEGINNING with the work of Houssay (1), there has accumulated a large body of evidence regarding the important role of the anterior lobe of the pituitary gland in carbohydrate metabolism (2). The severity of the experimental diabetic syndrome in the depancreatized dog can be alleviated by hypophysectomy and restored to its full-blown state by the administration of potent extracts of the anterior pituitary gland. More recently, Young (3) was able to produce permanent diabetes in dogs by the prolonged administration of large amounts of such extracts.

These facts have turned attention towards the possible influence of the anterior hypophysis in the etiology or on the clinical course of diabetes mellitus in man. The supposition that this gland might be involved has been supported by the fact that the postmortem examination of diabetics reveals little if any pathological change in the pancreas of most patients. However, evidence of morphological changes in the hypophysis of diabetic patients is also lacking.

Our approach to this problem depended upon the assumption that the possible hyperactivity of the anterior hypophysis in diabetics might be accompanied by an increase in vascularity and in size of the gland during life which would be difficult to detect postmortem. It therefore seemed worthwhile to attempt to obtain indirect evidence of pituitary enlargement during life from a study of the visual fields of diabetic patients.

Whether or not one might expect a purely physiologic enlargement of the hypophysis to reach such an extent as to encroach upon the optic chiasm is doubtful. However, Erdheim and Stumme (4) and others (5–10) have reported visual field changes in pregnancy, which they interpreted as resulting from physiologic hypertrophy of the pituitary. Both the results and the conclusions drawn from them have been doubted by other investigators (11–16). In view of this disagreement, it was obvious that negative findings as regards the visual fields of diabetics could not be interpreted as signifying the absence of pituitary hypertrophy. However, our work was instituted on the basis that positive findings might be significant.

METHODS AND RESULTS

In the Diabetic Division of the Mandel Clinic (Outpatient) of the Michael Reese Hospital, visual field studies were undertaken on a series of 65 patients. The method used was that of flash perimetry (17–19). This is essentially a modification of the accepted method of Walker and Cushing, whereby the visual stimulus is rendered quantitative and reproducible. An important feature of the modification is that it also tends to minimize subjective errors on the part of the patient, as in the classical method the patient may soon learn (from movements of the operator's arm, etc.) when to expect the approach of the visual object towards the periphery of his vision. But this does not occur in flash perimetry since only the operator knows whether the lamp has flashed or not. It is, therefore, very easy to check on a real or imagined response of the patient. Under these circumstances, while it is not intended to imply that the method of flash perimetry can detect earlier defects of the visual fields than does the classical method in expert hands, it is fair to say that one can be much more certain of the validity of any finding made by flash perimetry.

The patients were seen consecutively and no patient was eliminated from this series because of any

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complication, although it was necessary to retake the visual fields on several patients to confirm results. In 58 patients (90%), the peripheral extent of the visual fields was found to be entirely normal in spite of some minor complications found in the eye. Of these patients with normal visual fields, one had vitreous floaters and 6 had a few small hemorrhages and exudates. One patient had a pigmentary degeneration of the retina in one eye only; the visual field of this affected eye was reduced to 5° around the central fixation point. Keratoconus was noted in one cornea of a patient. Lens sclerosis, to the extent of causing a diagnosis of incipient cataracts, was found in 2 patients. One patient had been successfully operated upon for cataract in one eye, while another patient had had both eyes operated on.

The remaining 7 patients (10%), had visual field loss. In all a severe retinopathy was noted; in some the lesions were old and of long standing without any fresh hemorrhages or exudates; in others, only fresh lesions were noted; and in 4 patients the retina revealed both old and recent activity. Because of the character of the loss of peripheral visual fields the group of 7 so affected may be divided into 2 minor groups. *Group A*, consisting of 4 patients, had concentric contractions of the entire peripheral fields involving the nasal, as well as the temporal portions of the fields. In these patients it was found that the retinopathy was most extensive. *Group B*, consisting of 3 patients, had loss of only the temporal portions of the fields from the 80° to 60° meridians. The involvement in these cases was mostly in the nasal portion of the retina.

It is evident that only 3 out of our 65 patients exhibited visual field changes which might be interpreted as resulting from pituitary enlargement. One can only conclude that either most diabetic patients do not suffer an enlargement of the pituitary gland or that the enlargement, if it occurs, is not sufficient to encroach upon the optic chiasm to an extent detectable by perimetry.

The question arises as to whether the metabolic manifestations of the 3 patients with temporal visual field loss differed from those of the other diabetic patients in any way which might support the thesis that in the former the overactivity of the pituitary gland was the cause of, or contributed to, their diabetic state. With this in mind a parallel analysis of the case histories of all our diabetics had been conducted, without knowledge of the eye findings until the analysis had been completed. It seems unnecessary to go into great detail as to our methods in view of the largely negative nature of our results. Briefly, an attempt was made to classify the patients under various categories which might reflect the influence of endocrine factors in their past or present histories. The main classifications were as follows.

1. Direct evidence of pituitary disturbance such as acromegaly (For purposes of this paper Cushing's syndrome was also included.)
2. Evidence of thyroid disturbance
3. Family history of endocrine disturbances, including diabetes, dwarfism, etc.
4. Coincidence of diabetes with menopause, using less than 5 years difference in time as the maximum for coincidence
5. Menstrual difficulty before menopause, including also sterility and abortion of otherwise undetermined cause
6. Obesity—only if the diabetes was fairly well controlled
7. Hypertension, if disproportionate to the amount of arteriosclerosis noted

The patients were then classified in accordance with the number of the above categories into which they fitted. Finally each case was given a numerical value by arbitrarily weighting the significance of the above categories. A value of 3 points was placed on each of categories *1*, *2* and *3;* 2 points each on categories *4* and *5*, and 1 point each on categories *6* and *7*. If, for example, a patient's name appeared in categories *1*, *4* and *6*, the simple incidence of that case in our classification would be 3, while the weighted value of that case would be 6.

Using the above method it was expected that there would be a coincidence as regards the presence of visual field changes and the numerical ratings of our patients. Indeed, because of the small number of our cases which exhibited visual field changes the coincidence would have to be striking to be of significance. As a matter of fact, of the 3 patients who exhibited temporal visual field restriction only 1 had a high numerical rating.

SUMMARY

Perimetric studies in 65 unselected diabetic patients revealed a restriction of the visual fields in only 7 cases. Of these 4 showed concentric contraction of the entire visual field associated with extensive retinopathy while in 3 the loss of vision was in the temporal portion of the fields, accompanied by nasal retinopathy. Parallel analysis of the case histories yielded no correlation between the metabolic and endocrine characteristics and the visual disturbance. While the possibility is not excluded, our work has yielded no evidence that pituitary hypertrophy (or concomitant physiologic over-activity of the pituitary) is a factor in clinical diabetes mellitus.

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DIABETES

AN ATTEMPT TO DEMONSTRATE AN "ANTI-INSULIN" EFFECT OF BLOOD PLASMA OF CERTAIN DIABETIC TYPES

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THE PRESENT TREND in the study of human diabetes mellitus, resulting from the advance in knowledge of the humoral and neural regulatory mechanisms of carbohydrate metabolism, have forced a reconsideration of this symptom complex. This will undoubtedly lead to a sub-division of clinical types into classes in which the dysfunction of the various links in the metabolic chain will be used as the criteria for the etiology of the individual case.

Some attempts have been made to do this. Himsworth's (1) division of diabetes mellitus into insulin sensitive and insulin resistant types was in line with this reasoning. Griffiths (2) demonstrated a peripheral resistance to insulin in cases of hyperthyroidism. De Wesselow and Griffiths (3) found that the plasma of patients with diabetes mellitus over 40 years of age had a definite inhibitory action on the hypoglycemia produced when insulin was injected intravenously into fasted rabbits. The group of cases which showed this inhibition of insulin action most pronouncedly might be considered as mild basophilic or Achard-Thiers syndromes, associated as they were with obesity and hypertension. The plasma of young diabetics showed little or no inhibition. They believed that the rapid recovery of the blood sugar of the rabbits injected with insulin and plasma of the elderly group might be due to the presence in the plasma of some substance that directly inhibited the action of insulin. Or possibly, to a glycogenolytic body resembling the active principle of the anterior hypophysis described by Cope and Marks (4) which acts as a synergist to adrenalin in liberating glucose from liver glycogen. This latter supposition is rendered unlikely by the demonstration by Zucker and Berg (5) that demedullation in dogs does not affect the recovery from insulin hypoglycemia greatly, but that total adrenalectomy may delay this process considerably. If this be true, the insulin hypersensitivity of hypophysectomized (6) and adrenalectomized (7) dogs cannot be considered as due to a lack of epinephrin. It would seem more probable that the lack of the cortical hormone is the common denominator of this complex equation and that the inhibitory substance in the plasma of patients over 40 was the 'diabetogenic' or better 'glycotrophic' hormone of hypophysial or adrenal origin. Glen and Eaton (8) demonstrated this anti-insulin effect in their case of insulin resistance.

When De Wesselow and Griffith's method appeared, it seemed interesting to us to attempt to evaluate this test in cases which presented presumptive evidence of hypothalamic-pituitary or possibly adrenal involvement associated with diabetes mellitus. By its means some objective proof of the primary factor in these cases might be obtained. The method was modified slightly. Ten cc. of plasma from the 18-hour fasted patient was injected subcutaneously into a 24-hour starved rabbit weighing no more than 2 kg. The glucose content of the injected plasma was first determined by the Hagedorn-Jensen method, which method was used in all determinations. Three hours later the blood sugar of the rabbit was determined and 0.5 to 1.5 U. of commercial U40 insulin diluted to 1.5 cc. with saline was injected into the marginal ear vein. The dosage of insulin is noted in each instance on the curves. It was found that the 0.2 U. advised by De Wesselow and Griffiths was too small in our rabbits to produce a definite constant response. Blood sugar determinations were made at 15-minute intervals for one hour on blood from the ear veins and curves constructed of the response of the blood sugar to insulin as a function of time. The same rabbit suffered the same procedure as its own control one week later, the time interval permitting

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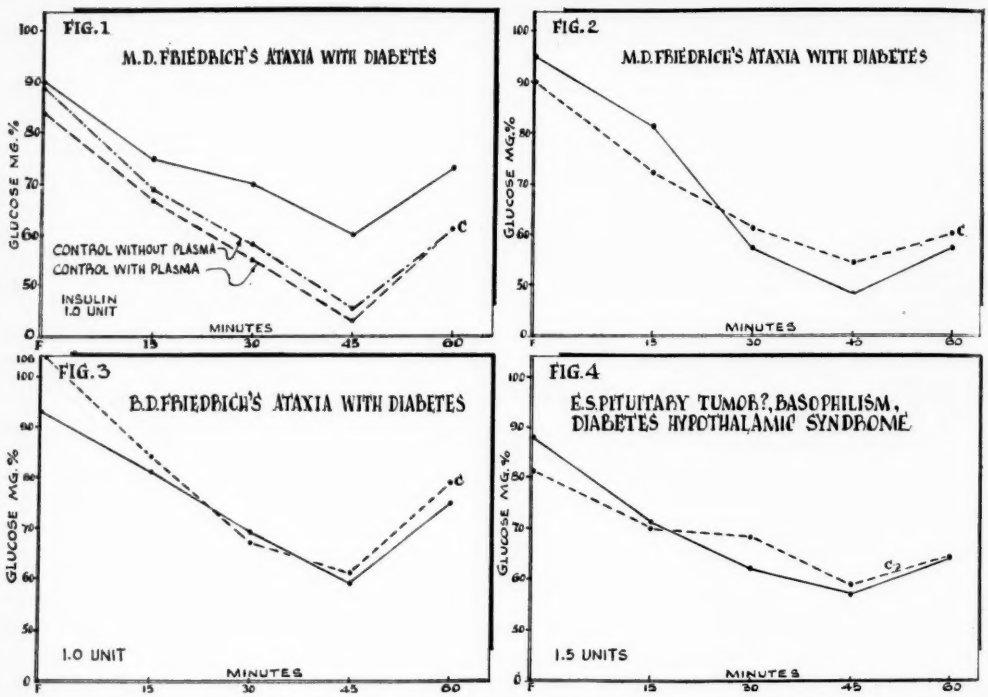


whatever effect might have been exerted by the plasma to have become dissipated. In the control experiment non-diabetic normo-glycemic plasma were used and glucose was added if necessary so that the plasma glucose contents of the control and experimental plasma was very nearly the same. A minute quantity of potassium oxalate was used as the anticoagulant. Insulin was withheld from those patients receiving it therapeutically for 24 hours if protamine zinc insulin was being used, and for 18 hours if regular insulin.

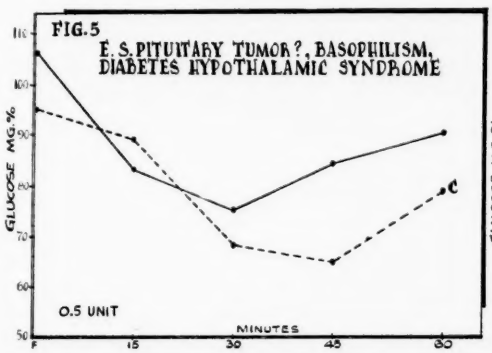
The first experiment with the plasma of a 23-year old female patient, *M.D.*, with Friedreich's ataxia and diabetes mellitus illustrates these points. In order to estimate non-specific effects of plasma, two controls were performed a week apart on the same rabbit, using 1 U. of insulin. It will be noted from figure 1 that the two curves coincide almost perfectly even though one has been preceded by the injection of plasma with added glucose to 240 mg. %, and the other had not. It seems obvious that the small amount of glucose (24 mg.) had no effect, but in the subsequent experiments a control plasma with added glucose if necessary was always injected in the control experiment to obviate any deviating factor in this respect. The upper curve represents the response of the same rabbit to the same dose of insulin when the patient's plasma was injected. There is a definite inhibition of the insulin action. Although the initial level of the blood sugar is nearly the same, the magnitude of the hypoglycemic response is markedly lessened and the rate is slowed, being most marked at the 45-minute level. This is fairly similar to the published curves of De Wesselow and Griffiths in their middle-aged groups. It led us to hope that this procedure would be successful in demonstrating an anti-insulin substance in the human plasma, for this case offers a good test object of the neuro-hypophysial theory, the diabetes presumably being due to the hypothalamic disease in Friedreich's ataxia. This viewpoint was concurred in by Dr. Kurt Goldstein, the neurophysiologist to the hospital. This case (*M.D.*) and that of her sister, *B.D.*, to be described later, form the subject of a paper by Schlezinger and Goldstein (9).

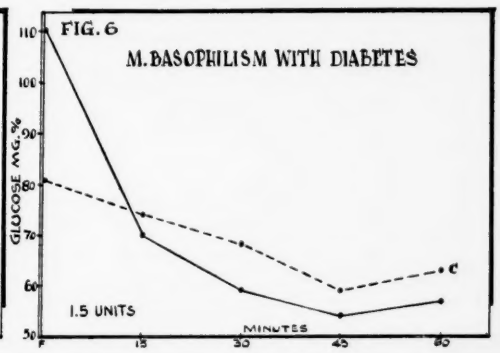
However, when this experiment was repeated, even though the diabetic status of the patient was the same, (the fasting blood sugars being 243 and 249 mg. % respectively) with no glycosuria and no change in the clinical status and at the same inter-menstrual period, the curve in figure 2 was the same. Now the experimental result is negative. The slight deviation from the control is probably ascribable to some variation in the rabbit and experimental error.

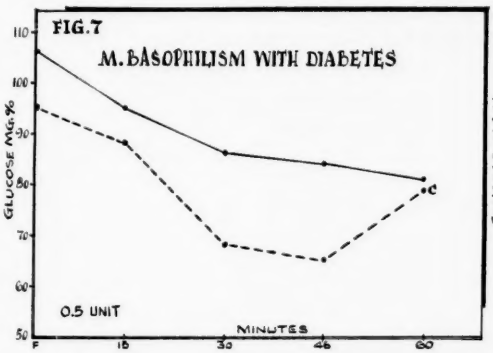
Fortunately, the six year older sister of this patient was available. She also has Friedreich's ataxia and

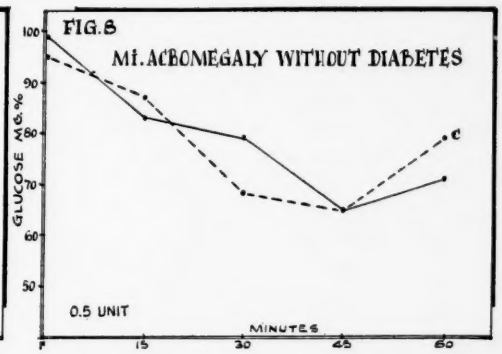
diabetes mellitus, and is a patient on the same service. Her curve is shown in figure 3. There seems to be no anti-insulin effect from her plasma. It is worthy of mention that on the day of experiment this patient's fasting blood sugar was 143 mg. %, as contrasted to that of her sister of 243 mg. %. This might represent a difference in her 'glycotrophic' hormone level.

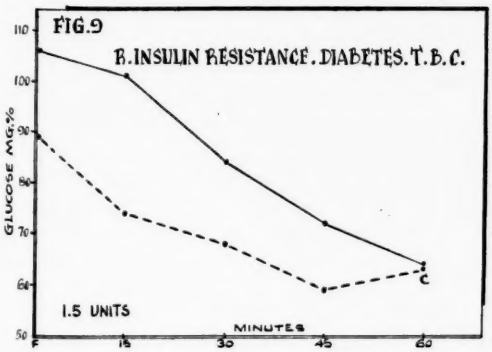
The next experiment was performed on a 39-year-old woman who has an obstructive lesion of the aqueduct of Sylvius, probably the result of luetic basilar meningitis. Deepening and widening of the sella turcica which, with the amblyopia due to optic atrophy secondary to papilledema, hirsuitism, amenorrhea, obesity, diabetes mellitus and hypertension led to the initial diagnosis of a pituitary tumor with the basophilic syndrome. However, in the opinion of Dr. Leopold Lichtwitz, it is more likely that the symptom complex is the result of unregulated hypophysial activity due to the destructive hypothalamic lesion from the internal hydrocephalus, thus simulating the basophilic syndrome. This curve with 1½ U of insulin was obtained while her fasting blood sugar was only 90 mg. %, and her diabetes was fairly mild, necessitating only 10 U. of insulin daily. It does not exhibit any insulin resisting factors.

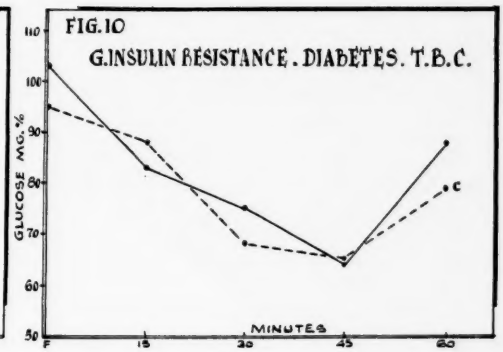












At a later date, when this patient's fasting blood sugar was 199 mg. %, the curve illustrated in figure 5 was obtained. On this occasion there seems to be some effect from her plasma, but if, as Himsworth (1) contends, one should interpret such curves only from the same initial blood sugar level, and one were to shift the experimental curve to the lower initial sugar level of the control, the difference would be much less marked. This could be done with several of the other curves and the similarity between the experiment and the control would be apparent.

Another case with the basophilic syndrome, obesity, hirsuitism, hypertension and diabetes in a 60-year-old woman was tested similarly on two occasions as illustrated in figures 6 and 7. In figure 6, the result is certainly not positive. In figure 7, there is possibly a slight decrease in the insulin effect after the administration of plasma. The same considerations as discussed in the previous cases would apply.

In figure 8 the curve of a patient with acromegaly without clinical diabetes is illustrated. The result is negative.

Figure 9 is the curve of the plasma of a man, about 55 years of age, with diabetes mellitus and tuberculosis who, during an episode of dermatitis, showed marked increase in his insulin requirement. The dermatitis was not due to insulin protein or pancreas protein. The result is negative.

The last curve is that of a 45-year-old man with pulmonary tuberculosis and diabetes who unexplainably developed a marked increase in his insulin requirement. As the curve shows, there is no evidence of an insulin inhibiting factor in his plasma.

The above results certainly do not warrant the assumption that this method demonstrates an insulin inhibiting factor in the plasma of these patients with the possible exception of the first case. These cases theoretically should have exhibited such a factor for they exemplify several of the various syndromes in which anti-insulin effects are assumed to be present. All it signifies is that the method does not demonstrate it.

When one considers the multitude of factors involved in such tests it is quite obvious that a clear result could not be obtained excepting possibly as a statistical average from a large series of experiments, such as in the report by DeWesselow and Griffiths (3). If one may paraphrase the statement of Holmes (10) that "a normal sugar tolerance curve is the result of many factors, an intricate balance of endocrine secretions, the state of the enzyme systems in the various tissues and the fulness or depletion of carbohydrate stores in the liver and perhaps elsewhere," and substitute "an insulin resistance curve in a rabbit" for sugar tolerance curve, the comparison is appropriate.

In our experience, therefore, the test cannot be applied to the individual case and we must await a a better method for the clinical estimation of the primary effect in diabetes mellitus. Possibly the procedure suggested by Campbell (11) for determining the anterior pituitary factor which increases liver fat and causes increased liver glycogen and insulin resistance (glycotrophic effect) might be used clinically, although it demands the statistical analysis of a large series of mice. Jensen and Tolksdorf (12) report the use of this method as a test object for the activity of adrenotropic and adrenal cortical preparations. They state that these substances produce a definite glycotrophic (anti-insulin) effect. However, it is far from a simple clinical procedure.

It would seem logical in the present welter of confusion regarding the neuro-humoral control of metabolism to await further clarification before a clinical sub-division of diabetes mellitus can be made objectively. Perhaps, as Thomson and Collip (13) suggest, the pituitary factor of O'Donovan and Collip (14), presumably from the pars intermedia, may be the metabolic hormone responsible for the glycostatic, glycotrophic, and ketonemic effect of anterior pituitary preparations. It would certainly simplify matters if this be confirmed and reduce the anterior pituitary action on carbohydrate metabolism producing hyperglycemia and glycosuria to three methods: (*a*) a depression of islet tissue which may become irreversible, (*b*) by stimulating the adrenal cortex, and (*c*) by some direct action such as abolition of carbohydrate oxidation.

It seems logical to conclude that human diabetes mellitus is a complex disease probably of multiple origins depending on whatever link in the metabolic chain is affected, from the grosser hormonal and nervous regulatory level to the fundamental stage of cellular oxidations. When the exact mode of action of the regulatory agents (hormonal and nervous) on the metabolism of the effector cell is understood, we shall be able to transfer our concepts to a cellular basis, an effector basis. Time will give us means of determining what factor or factors are involved in the individual case.

At the time of the preparation of this manuscript an article appeared (15), using the De Wesselow and Griffiths method in determining insulin resistance in middle aged diabetics. Their results, excepting in 2 of 5 instances of insulin resistance in the patients tested, do not show the presence of substance in the plasma inhibiting hypoglycemic action of insulin. This is in accord with findings reported above.

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THE CALORIGENIC ACTION OF THYROID SUBSTANCE IN OBESE PATIENTS

OBESITY

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IN THE TREATMENT of obesity much confusion exists concerning the use of thyroid substance. This was originally created by Von Noorden (1) who claimed that obesity was due to thyroid deficiency and assumed a substitutional value to thyroid therapy. Many studies have since shown that hypothyroidism is only a relatively small factor in the development of obesity. In fact, myxedematous patients who are thin or of normal weight are not infrequent, and cases described as non-myxedematous hypothyroidism are usually underweight (2). Gordon (3) in a study of obesity in childhood, found only 6% that he classified as primary hypothryoidism. Lyon and Dunlop (4) also found a small number among obese adults. Spriggs (5)found only 15% of his obese patients with B.M.R.'s lower than normal. Obesity is no longer considered due to hypothryoidism alone and thyroid therapy cannot be considered substitutional treatment in all cases.

Recently Strang and Evans (6) as well as Short (7) have pointed out that obese patients actually have elevated B.M.R.'s when these are calculated on the basis of ideal weight instead of actual weight. The use of thyroid as an adjunct to treatment is stated to be contraindicated at the onset of treatment because the B.M.R. would be further raised. Such a viewpoint presupposes that obese patients respond to thyroid administration with increased heat production.

MATERIAL AND SCOPE

This study was undertaken to investigate the actual calorigenic action of thyroid substance when orally administered to obese patients. In all, over 100 cases of obesity were treated and many single B.M.R.'s were obtained after the administration of thyroid substance. Only those patients in whom repeated B.M.R. determinations were made are reported. The willingness on the part of the patient to cooperate formed the only basis of selection.

TABLE 1. *Case 1*

Date	Medication	Daily dose	Duration	Wt.	O_2 Consumption	B.M.R.
1935				lb.	cc.	%
12/17	Thyroid (Armour)	2 grains	8 wk.	122½	240	+26
12/24	Thyroid (Armour)	1 grain	1 wk.	122½	197	+ 4
1936						
1/ 7	Thyroid (Armour)	1 grain	2 wk.	124½	198	+ 2
1/21	Thyroprotein	50 mg.	2 wk.	122½	236	+24
2/ 4	Thyroprotein	25 mg.	2 wk.	122½	201	+ 5
3/17	Thyroprotein	25 mg.	6 wk.	126½	191	− 2
6/11	Thyroid (Armour)	1 grain	3 mo.	130	165	−16
8/ 4	Thyroprotein	25 mg.	7 wk.	128	221	+14
10/ 6	Thyroid (proprietary)	25 mg.	7 wk.	133	193	− 3½
11/17	Thyroid (proprietary)	25 mg.	6 wk.	128½	197	+ 1[1]
1937						
1/ 7	Thyroid (proprietary)	50 mg.	7 wk.	130	177	−10[2]
2/ 8	Thyroid (Armour)	1½ grains	4 wk.	127½	201	+ 3

[1] The patient complained that she was not as active, but no change was found on examination.
[2] The patient showed puffed eyes, felt sluggish, slightly constipated.

The thyroid preparation used was a thyroprotein standardized by the method of weight loss induced when administered to guinea pigs. This preparation contains 0.4% to 0.6% iodine and is dispensed in 25 mg. tablets.[1] Large doses of the thyroid substance were administered following the methods of the con-

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[1] Thyroprotein, in the form of thyractin, was supplied through the courtesy of the Winthrop Chemical Co., New York City.

TABLE 2. *Case 2*

Date	Medication	Daily dose	Duration	Wt.	O_2 Consumption	B.M.R.
1935				lb.	cc.	%
10/12	No treatment			172	181	−25
10/19	Thyroprotein	150 mg.	1st wk.	172	255	+ 5
10/26	Thyroprotein	150 mg.	2nd wk.	169	240	0
11/ 2	Thyroprotein	150 mg.	3rd wk.	168½	235	− 2
11/ 9	Thyroprotein	150 mg.[1]	4th wk.	167½	259	+ 8
11/16	No medication		1st wk.	168	212	−11½
11/23	No medication		2nd wk.	168	193	−19½
11/30	Thyroid (P.D.)	1 grain	1 wk.	168	197	−18
12/28	No medication		4 wk.	175	191	−21½
1936						
1/11	Thyroid (P.D.)	3 grains	2 wk.	175	211	−13½
2/ 1	Thyroid (P.D.)	4 grains	2 wk.			
		3 grains	1 wk.	175	227	− 5
9/12	No medication for months (strict dieting)			165	187	−21

[1] On the 19th day of medication, patient felt "shaky." She omitted medication on that day. On 20th day, she took 75 mg. without symptoms and then resumed 150 mg. a day.

tinental authors (8) who advise larger doses than are customarily employed in this country.

In order to compare the calorigenic action and potency of the thyroprotein used in this study with another standard preparation, a patient with myxedema served as a test case. In this case the substitutive efficiency of 25 mg. of the thyroprotein was slightly stronger than one grain of desiccated thyroid (U.S.P.).

Case 1 Myxedema. Mrs L., a 43-year-old Jewish housewife, had noted that for the previous 4 years she was sluggish, her speech became slurred, she had to sleep several times a day and she was very constipated. Physical examination revealed a typical case of acquired myxedema. Her initial B.M.R. was −46; height 63 in.; weight 132 lb. Following thyroid administration, her symptoms and appearance were transformed in a fashion usually seen when myxedema is treated. The study was reported in table 1 and started after the myxedematous condition had cleared up and she was on a maintenance dose of 2 grains of desiccated thyroid a day.

Types of Calorigenic Responses to Thyroid Therapy

In myxedema and hypothyroidism, the oral administration of thyroid substance has been shown to elicit calorigenic responses which seem to follow a more or less constant pattern. The literature concerning myxedema has been summarized by Means (9) and a comprehensive exposition of the treatment of nonmyxedematous hypothyroidism has been given by Berkman (10). However, in individuals with normal thyroid function, the effect of the administration of thyroid substance was found to be variable. Early work [literature summarized by Magnus-Levy in 1907 (11)] demonstrated that some reacted with an elevation of the metabolic rate and others showed no increase in oxygen consumption. Much of this work was disbelieved because of the lack of standardization of the thyroid preparations used. However, the careful studies of Grafe (8) in 1923 not only substantiated these results but showed that the variable effects depended on the individual susceptibility of the patient rather than on other factors such as lack of potency and lack of absorption or destruction of the hormone in the intestinal canal.

From the viewpoint of thyroid therapy in obesity, the patients were grouped into two main classes.

(1) Obesity with hypothyroidism
(2) Obesity without hypothyroidism
  (*a*) Thyroid sensitive group
  (*b*) Thyroid resistant group

Obesity with Hypothyroidism

As was stated above, the instances of obesity associated with thyroid deficiency consist of only a small number in the general run of obese patients. In the many series mentioned above, the frequency of its occurrence varied from 6% to 15%. In the patients reported in *cases 2* and 3 the basal metabolic rates increased in response to thyroid medication and decreased on discontinuing the latter. The menstruation became normal and both patients volunteered the information that they were less fatigued and more active when on medication. Clinically it was the alleviation of the numerous symptoms and signs of thyroid deficiency that substantiated the diagnosis. A maintenance dose of 75 to 100 mg. of thyroprotein daily was needed to maintain the level of the basal metabolic rate near normal as well as to retain the clinical improvement. This requirement is the same as in myxedematous patients except that larger doses of thyroid are needed. Our results are similar to those of Brown and Shea (12) who found that 100 to 150 mg. thyroprotein daily were needed to keep the metabolic rate of a patient with hypothyroidism at a normal level; this dose compared in potency to 10 to 15 grains of "thyroid" and 2/80 to 4/80 grain of thyroxin orally.

The weight losses in the 2 cases reported here were

small despite medication when the patients did not adhere to very restricted diets. The administration of thyroid substance sufficient to raise the metabolism 15% to 25% for prolonged periods of time did not substitute for dietary restriction. Strang and Evans (13) noted this same finding when they compared the amount of weight lost by patients who were on controlled periods of dieting alone with the weight lost when the metabolic rate was markedly elevated by dinitrophenol. The weight lost by the patients of these observers was not increased by raising the metabolic rate. Bayer and Gray (14) also found that dietary control was needed to achieve results with thyroid therapy.

Case 2. Obesity with hypopituitarism and hypothyroidism. Miss E. R. was 17 years old, a student dietitian. Her height was 66 in., weight 175 lb. The patient had been stout for 9 years. Her menses were always irregular, skipping 2 or 3 months. She was easily fatigued and was troubled with constipation. The physical examination was non-contributory aside from the obesity which was distributed all over the body but particularly in the girdle region. The skin was not dry and the pulse rate was usually 70; her hair was thin. Results of treatment with thyroid substance are given in table 2.

Case 3. Localized obesity and hypothyroidism. Miss F. A., a 20-year-old college student, height 63 in., had had since childhood thighs that were disproportionately obese. There were many creases on both thighs, and the portion above the knees overhung the joint. She had been treated by physiotherapeutic measures, diet, etc. in childhood without results. The rest of the body including the buttocks, hips and ankles were of relatively proportionate size. Upon entering college, the B.M.R. was found to be "very low." In addition she was easily fatigued, her menses were scanty and irregular, skipping six months at a time. She was very constipated. She was given oral desiccated thyroid substance and injections of Antuitrin for several months with improvement of symptoms and a return of normal, regular periods with a 28-day cycle. She had not lost weight despite adherence to a 1,400-calorie diet. In November 1934, she changed residences and physicians. She had not had any medication for several months and there was a return of all symptoms except that the menses remained normal. She was given thyroprotein in courses of 75 to 125 mg. a day for 2 to 3 weeks and one week without medication. She was also given an 1,100-calorie diet to which she adhered rigorously. A review of the calorigenic response is given in table 3. The B.M.R.'s were usually determined at the end of a period of medication and before a rest period.

Obesity without Hypothyroidism

Exhaustive studies by Grafe (15) have shown that irrespective of the original B.M.R., obese patients behave as normal people and show all ranges of responses to thyroid administration from marked intoxication to absolutely no reaction at all. H. Zondek (16) claims that in the "majority" of patients with obesity, thyroid administration raises the metabolism in the same fashion as in myxedema cases, but he further states "yet in some patients, particularly certain cases of pituitary or genital obesity, thyroid exerts hardly any influence on metabolism. Even some cases of thyrogenic obesity prove refractory."

Much confusion exists as to the relative frequency of this thyroid sensitivity and insensitivity. In animals most workers have found little refractoriness to thyroid. Wyatt, Weymueller and Levine (17) found that all of their 7 studied cases of infants under 18 months of age uniformly showed a calorigenic response to thyroid administration. Topper and Cohen (18), however, found in the older pediatric group that in 9 normal children the administration of 15 grains of thyroid substance (whole gland) daily, did not increase the B.M.R. nor give evidences of toxicity after months of medication. The obese cases reported in this study show that all ranges of response can be found irre-

TABLE 3. *Case 3*

Date	Thyroprotein, daily dose *mg.*	Duration	Wt. *lb.*	O_2 Consumption *cc.*	B.M.R. %
11/10/34	No treatment		136½	175	−17
Interim[1]	75	3 wk.—1 wk. rest			
3/ 2/35	No treatment	1 wk.	132½	171	−19
Interim[1]	75	4 wk.—2 wk. rest			
10/12/35	75	4 wk.—no rest	138½	196	− 8
Interim[1]	75	4 wk.—1 wk. rest			
1/16/36	100	4 wk.—no rest	142½	201	− 7
Interim[1]	125	4 wk.—2 wk. rest			
5/17/36	150	2 wk.—no rest	143½	210	− 3
Interim[1]	150	3 wk.—1 wk. rest			
7/18/36	150	3½ wk.—no rest[2]	131½	214	+ 2
9/19/36	100	8 wk.—no rest[2]	126	212	+ 3
Interim[1]	75	10 mo.—no rest			
7/ 5/37	No treatment	2 wk.	136¼	181	−11(N.S.)[3]
1/ 7/38	100	6 mo.—no rest	134½	204	0(N.S.)[3]

[1] Periods when given thyroprotein with rest intervals of no medication as indicated; B.M.R.'s not determined.
[2] Periods of extremely rigorous dieting with 900 calories.
[3] N.S. = New Mayo Standard (1936).

spective of the initial B.M.R. and irrespective of the type of obesity.

Thyroid Sensitivity

In addition to dietary restriction, our cases of obesity were given 75 to 150 mg. of thyroprotein daily for a period of 10 to 21 days followed by a rest interval of 5 to 7 days before therapy was again started. In over one hundred cases treated in this manner, 8 cases showed signs of toxicity within the first week. The toxic symptoms included nervousness, palpitations, faintness, tremor, diarrhea, weakness, sweating to excess, and headache. An interesting fact was the early appearance of these symptoms. Mosler (19) also commented on the rapid appearance of the toxicosis within a few days after his patients took their thyroid-containing medication for weight reduction. In the literature, the occurrence of sensitivity to thyroid administration has been noted frequently but few determinations of its relative frequency have been reported. Weisman and Reifer (20) found among 20 obese women treated with thyroid substance only one who showed toxic symptoms at the end of a week; this case had received the least amount of thyroid given in the group. We found a slightly higher incidence of such extreme sensitivity among obese patients.

The findings of Morris (21) must be mentioned; he reported 4 thyrocardiacs with B.M.R.'s ranging from -32% to -7%. This suggests the possibility that local sensitivity may occur. All of our patients were under the age of 50 years; possibly in older patients evidence that local sensitivity, such as cardiac symptoms, may occur without any remarkable systemic toxic symptoms. In our series there were 2 patients who complained of severe headaches on the day following the onset of thyroid therapy; the cephalea disappeared when the medication was discontinued. One of these patients allowed herself to be studied, taking 10 grains of aspirin 4 times a day to relieve the headache. At the onset her weight was 243 lb. and her B.M.R. was -8%. After 75 mg. thyroprotein a day for one week, her B.M.R. rose to $+2\%$ and she lost 4 lb. in weight. Since the headache started on the second day, it seemed independent of the calorigenic action of the thyroid substances. These cases with headaches were the only ones wherein a "localized sensitivity" existed.

We were able to study the calorigenic response to thyroprotein administration in 3 'thyroid-sensitive' cases. *Case 4* demonstrated a constant response to the same dose of medication, the toxic symptoms coming on the seventh day. *Case 5* showed the rapid rise of the B.M.R. after medication, and the rapid fall to normal within 10 days after its discontinuance. *Case 6* was interesting because of the initial low B.M.R. although the patient had no clinical signs nor symptoms of hypothyroidism. She demonstrated marked sensitivity which developed slightly later than the other two cases.

Plummer (22) introduced the concept that the effect of thyroid extract varies inversely with the amount of secretion of the gland. Hoskins (23) suggested a therapeutic test of thyroid deficiency based on the calorigenic response to thyroid administration in patients with diminished thyroid function. The cases reported here show that thyroid lack is not the only factor involved in such sensitivity.

Case 4. Marked obesity; thyroid sensitive. J.O.D., male college student, age 24 years, weight 271 lb., height 69½ in. had had generalized distribution of adipose tissue with markedly accentuated girdle fat since childhood. Sex characteristics were normal; he had always had marked vasomotor instability. The patient always felt "light headed," weak, and noticed a tremor on the seventh day of the medication. He was on a restricted food intake (1,500 calories) during the period of study. The diuretic effect of the thyroid substance was most marked. He originally had a blood pressure of 200/110 which dropped with treatment to 170/90.

Case 5. Moderate obesity; thyroid sensitive. Mrs. J. K., a 47-year-old housewife, height 61½ in., had always been stout but had insidiously gained 15 lb. during the past few years without changes in dietary or other habits to explain the gain in weight. The rest of the history was negative aside from the fact that her mother had exophthalmic goiter. The physical examination and laboratory data were also essentially negative. She remained on a high protein, 1,000-calorie diet, and was given 150 mg. of thyroprotein, q.d. A marked diuresis occurred and on the fifth day the patient complained of marked palpitations, tremor, nervousness and weakness. She lost 4 lb. in this time. Medication was discontinued for one month and then the therapy reported in table 5 was instituted. She observed a 1,000-calorie diet throughout.

Case 6. Moderate obesity; thyroid sensitive. Miss G.T., 26-year-old secretary, height 63 in., had weighed from 165 to 170 lb. ever since the age of 12 years. During the

TABLE 4. *Case 4*

Date	Thyroprotein, daily dose *mg.*	Duration *days*	Wt. *lb.*	O_2 Consumption *cc.*	B.M.R. *%*	Toxic symptoms
4/ 3/38	No medication		271½	341	+ 4	0
4/10/38	150	7	268½	400	+22	+ 7th day
Interim	No medication	7	268	—	—	0
4/25/38	150	7	—	—	—	+ 7th day
6/ 5/38	No medication	10	250	—	—	0
6/12/38	150	7	253	415	+29	+ 7th day

TABLE 5. *Case 5*

Date	Thyroprotein, daily dose *mg.*	Duration	Wt. *lb.*	O_2 Consumption *cc.*	B.M.R. %
9/15/35	No medication	1 mo.	154½	191	− 7
9/18/35	125	2 days	152½	204	0
9/24/35	125	6 days[1]	151	247	+21[2]
9/27/35	No medication	3 days	150½	237	+16
9/30/35	No medication	6 days (total)	150½	210	+ 3
10/ 4/35	No medication	10 days (total)	151½	192	− 6
10/ 9/35	160	5 days	151	235	+15

[1] The patient felt "shaky" on the sixth day and thyroid therapy was stopped.
[2] Toxic symptoms had appeared on the previous day.

past 10 years she had constantly "watched her food" to avoid gaining weight. She had placed herself on many of the fad diets and had lost a few pounds but she always regained her weight soon after going on a balanced diet. Her menses were normal, and the remainder of her history was non-contributary. Physical examination revealed only a generalized fat distribution and marked vasomotor instability due to the embarrassment of a physical examination. All signs and symptoms of hypothyroidism were absent. The course of treatment is summarized in table 6.

The reactions noted by this patient consisted of tremor and general nervousness ("jittery"). The pulse rate, which was extremely labile because of vasomotor instability, was no more so when examined during the periods of thyroid medication. Only on one occasion did she have palpitations. All symptoms disappeared when the medication was stopped. There was no change in the blood pressure which remained at 122–118/68–72. The diuresis and sweating were tremendous; in fact, the patient was embarrassed by the frequency of urination. When seen one year later, the patient had regained all her lost weight despite the fact, as she claimed, she had restricted her food intake generally.

Insensitivity to Thyroid Substance

The majority of our patients showed little or no effects after taking large doses of thyroid substance for periods of time as long as 3 to 4 weeks. Insensitivity to thyroid administration has been recognized for a long time. As early as 1895, Becker (24) reported a normal child who swallowed 90 5-grain tablets (whole gland) of potent thyroid substance without any observed effects. Apparently insentivity is a term of only relative significance. Several factors are involved, including (*a*) the strength of the preparation, (*b*) the size of the dose, (*c*) the length of time of administration, and (*d*) the reactiveness of the patient.

There are other reports similar to Becker's case, concerning the relative harmlessness of single tremendous doses (25). Prolonged medication with large doses may also give no harmful results. The classical case of Aub and Stern (26) showed this. A 24-year-old girl with heart block took 2,000 grains of thyroid (whole gland) over a period of 3 to 4 months. She had been taking 26 to 28 grains daily for 3 weeks previous to a B.M.R. determination which was +47%. There were no toxic symptoms and no loss in weight; the cardiac rate was increased. It took 3 weeks for the metabolism to return to normal, and during this time she gained 8 lb. Another classical case, described by Notthaft (27), is illustrative of how massive doses can overcome apparent refractoriness. A male patient took 1,000 1-grain tablets (whole gland) in 5 weeks. After the third week only he began rapidly to develop acute hyperthyroid symptoms. On discontinuing, the symptoms disappeared with the exception of eye changes and a goiter which lasted 6 months. Bram (28) has reported his experiences when inducing ther-

TABLE 6. *Case 6*

Date	Thyroprotein, daily dose *mg.*	Duration *days*	Wt. *lb.*	O_2 Consumption *cc.*	B.M.R. %	Toxic symptoms
6/ 9/35	No medication		165	190	−16	0
6/15/35	100	6	160	—	—	0
6/24/35	100	14	159	—	—	+ for 4 days
6/30/35	No medication	6	156	—	—	0
7/15/35	100	14	154½	—	+22	+ for 1 day
7/20/35	No medication	5	—	—	—	0
7/29/35	150	9	153	—	—	+++ for 1 day
Interim	No medication	20	150	186	−12	
8/26/35	150	8	149	—	—	0
9/ 4/35	No medication	8	150	—	—	0
9/15/35	150	11	147½	317	+69	+++ for 1 day
9/22/35	No medication	6	149	250	+19	0
10/ 6/35	150	14	150½	277	+31	+ 1 day

Thyroid medication stopped.

apeutic hyperthyroidism, giving in his protocols the results in 4 cases of obesity. Three of these cases (*cases 6, 8, 9*) had initial B.M.R.'s of −34, −22 and −28% respectively; it took 10 to 14 weeks of medication (4–9 grains desiccated thyroid daily) to bring their metabolisms to within normal range. When the metabolisms were further raised to as high as +18%, no toxic symptoms ensued. Despite the low initial B.M.R.'s these cases did not show the typical hypothyroid therapeutic response as described by Berkman (10) or as illustrated by our *cases 2* and *3*. They better illustrate the overcoming of thyroid insensitivity by prolonged massive doses of the drug.

Swaim (29) and Hall and Monroe (30) in treating arthritics with thyroid substance found in some cases a drop in the B.M.R.'s after prolonged medication. The latter authors found that the B.M.R.'s of 44% of their patients showed no change and in 11% showed an actual drop. Two cases in our series (*cases 14* and *15*) demonstrated this same fall in the metabolic rate after medication from +17% to lower rates. They also showed that insensitivity to thyroid may be present in patients with high initial B.M.R.'s as well as low B.M.R.'s as mentioned above.

The following case reports of ambulatory patients undergoing treatment and cooperating sufficiently to enable careful studies of the metabolic rate, illustrate all the factors mentioned. *Case 7* showed a delayed calorigenic response to thyroid medication after 4 weeks, demonstrating the importance of a time factor. *Case 9* showed a calorigenic response to larger doses whereas the patient seemed insensitive when given smaller doses, illustrating the role played by the smaller dose. The remaining cases show the relative refractoriness of the majority of our patients in contrast to the thyroid-sensitive and hypothyroid groups mentioned above. *Case 10* showed that this refractoriness occurred in the same patient for at least two years.

Case 7. Miss R.B., a 27-year-old girl, who because of her short stature, 54 in., felt that she had to lose weight. She had been "skinny" until the menarche when she gained up to 120 lb. At that weight level she appeared overweight and she had tried to lose weight ever since with no success. Unlimited eating for short periods of time led to quick gains in weight which were difficult to lose. The examination results and laboratory data were essentially negative, aside from a B.M.R. of −15%. Table 7 shows the course of treatment. She was adhering to a 900-calorie high protein diet throughout.

TABLE 7. *Case 7*

Date	Thyroprotein, daily dose *mg.*	Duration *weeks*	O_2 Consumption *cc.*	B.M.R. %	Wt. lb.
7/ 7/36				−14[1]	
7/ 7/36	No medication		155	−15	120½
7/15/36	150	1	151	−14	117½
7/22/36	150	2	146	−20.5	117½
8/ 5/36	150	4	182	+ 1.5	113½
8/12/36	150	5	196	+ 8	114½

[1] B.M.R. taken in another laboratory. Toxic symptoms (slight) on 34th day consisting of feeling weak and "shaky"; blood pressure and pulse rate were within normal range.

Case 8. Mrs. Y., a 45-year-old social worker, who had been obese since the birth of her children, was extremely nervous and prone to hysterical episodes. Her B.M.R. was always normal and her blood pressure had always been found to be low. Strict dieting created a status of asthenia and at one time hyperinsulinism had been diagnosed but could not be substantiated by blood sugar determinations. Several years before she had been given small doses of thyroid for at least 6 months; she never had toxic symptoms and did not lose weight at the time. The menses were normal. Examination revealed an obese woman, height 65½ in., a pituitary type of fat distribution, tapering fingers, a blood pressure of 95/50, a labile pulse rate ranging from 76 to 90 per minute. Otherwise the examination results and essential laboratory data were negative. She was put on an 1,800-calorie diet, which was a comparative reduction of food intake, without increased weakness. She lost 5 lb. in 2 weeks; the weight then was stationary for 2 weeks. She was studied as follows.

TABLE 8. *Case 8*

Date	Thyroprotein, daily dose *mg.*	Duration *weeks*	Wt. lb.	O_2 Consumption *cc.*	B.M.R. %
2/ 6/37	No medication		227	258	− 1.5
2/13/37	100	1	224	283	−10.5
2/20/37	100	2 (total)	221½	256	− 2
2/27/37	100	3 (total)	220	284	−13.5
3/ 6/37	100	4 (total)	217	260	− 4.5

This patient was emotionally upset during the entire time that she was studied. It was for this reason, we believe, she had variable metabolic rates. There was an excellent diuretic response during the thyroid treatment. During the course of treatment her blood pressure rose to 120/68 and she no longer had "hunger spells." She maintained a higher dietary restriction than ever before, even though her diet contained 1,800 calories. She was finally kept on 150 mg. thyroprotein a day, for 2 weeks, with a 1-week rest interval between courses and continued to lose down to 200 lb. when she discontinued treatment.

Case 9. Miss F.R., age 29, an unmarried salesclerk, height 69 in., had been obese since childhood. At the age of 13 she gained to 200 lb. In 1935 metabolic rate was found to be −18%. She had been taking thyroid extract intermittently in small doses for 5 years; none for 8 months previously. She had marked vasomotor symptoms when "nervous," (cold hands, pallor, faintness). Otherwise there were no complaints. Menses were regular. Her mother was a diabetic. Examination results were negative aside from the obesity. The adipose tissue was generally distributed over the body; forearms and legs were thin. The study with administration of thyroid substance is given in table 9.

Weight Reduction

Many careful statistical studies have shown the value of thyroid therapy in accelerating weight loss

TABLE 9. *Case 9*

Date	Thyroprotein, daily dose mg.	Duration	Wt. lb.	O_2 Consumption cc.	B.M.R. %
5/ 6/38	No medication		194	231	− 7
6/ 2/38	75	1 wk.	191.5	224	− 9
6/ 9/38	75	2 wk. (total)	191.5	231	− 7
6/17/38	75	3 wk. (total)	188	223	−10
	No medication	2 wk. (total)	—	—	—
7/19/38	150	18 days	183	275	+11.5

There were no toxic symptoms or signs.

after diet therapy becomes ineffective (4, 14). This was substantiated in over one hundred patients not reported here, who had previously become discouraged by an apparent inability to lose weight. The administration of thyroprotein gave very much better results and these concrete decreases in weight were far more valuable in encouraging the patients to remain strictly on their diets than the exhortations of the physician. Weisman and Reifer (20) have reported their successes in reducing the weight of 20 patients originally weighing over 200 lb., obtaining weight losses of from 20 to 50 lb. in 3 months. These patients were given orally 1 to 9 grains of desiccated thyroid daily; no toxicity but a tremendous diuresis was noted and the authors advocated the use of the diuresis as a guide to the dosage of thyroid used. The diuretic action of the thyroprotein was noted in our patients in whom no calorigenic effects were observed. The results were similar to those found by A. A. Epstein (31) in nephrotic patients when large doses of thyroid substance were given.

The fluid balance factor in the obese patient, as pointed out by Newburgh (32) plays an important role when the patient is attempting to reduce. That the water retention factor may not be secondary but an essential characteristic of marked obesity has been noted by Zondek (16) who classifies a special ill-defined group which he calls "cerebral-pituitary-salt-water obesity." Rowntree (33) has also shown the value of employing salyrgen in the reducing regimes of several patients when diet seemed comparatively ineffectual. This clinical aspect of obesity can be successfully treated with thyroid therapy particularly in patients who are relatively insensitive to the calorigenic and toxic effects of thyroid substance. Courses of large doses for a short period of time (14–20 days) with interval rest periods (1 week) can be carried on in the majority of patients without harmful effects.

SUMMARY

Cases of obesity associated with hypothyroidism exist, but these are relatively few of the obese cases and are usually diagnosed by the associated clinical hypothyroid symptoms. They are treated as cases of hypothyroidism.

Other cases of obesity, irrespective of the initial B.M.R., respond to the administration of thyroid substance as reported in non-obese cases. This may be with marked sensitivity, marked insensitivity, or an intermediate degree of sensitivity. The majority of patients show the last two types of responses.

The thyroid sensitive patients show signs of toxicity very soon after the onset of treatment. The majority of the other cases can be given large doses of thyroid for short intervals of time (14–20 days) with a relatively slight or no calorigenic effect; diuresis is usually noted. A short interval of rest from medication allows resumption of treatment without altering the thyroid resistance.

There is evidence to show that much of the effect of thyroid substance in weight reduction comes in the absence of calorigenic action.

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ADDENDUM

Case 10. Mrs. F., 41-year-old housewife, height 60¼ in., showed genital obesity, onset following panhysterectomy 15 years before. Adipose tissue was chiefly confined to buttocks and thighs. The

patient was seen at intervals and treated sporadically. Her initial B.M.R. was −8% and her weight was 188 lb. In December 1937, after taking 150 mg. of thyroprotein a day, for 2 weeks, the B.M.R. remained −8%. In February 1938, 10 days after taking a similar dose, her B.M.R. was −6%. In January 1939, a B.M.R. was found to be −8% after a 14-day course of the same medication. In this case there was a little diuresis. Dieting was sporadic, 11 lb. was lost in this time.

Case 11. Miss E.D., a 22-year-old student, unmarried female, height 62 in., had been obese (200 lb.) at the age of 16 years. Menses were normal. She had been treated with thyroid orally and pituitary substance by injections in the past. Adipose tissue was generally distributed. She was on a 1,200-calorie diet throughout treatment. Marked increase in perspiration but little diuresis was noted during treatment.

Date	Thyroprotein, daily dose mg.	Duration weeks	Wt. lb.	O_2 Consumption cc.	B.M.R. %
12/20/36	No medication		183	254	+ 9
1/ 3/37	100	1	179	253	+ 9
1/10/37	100	2	173½	253	+10
1/17/37	100	3[1]	173	268	+17
1/24/37	No medication	1	171	242	+ 7
1/31/37	No medication	2	171½	226	0
2/21/37	100	3	165½	240	+ 6

[1] Patient had a slight cold for a few days, no fever, no toxic signs.

Case 12. Mrs. I.B., a 36-year-old housewife, height 61 in., had exogenous obesity. She was put on a 1,500-calorie diet.

Date	Thyroprotein, daily dose mg.	Duration weeks	Wt. lb.	O_2 Consumption cc.	B.M.R. %
4/ 9/37	No medication		165½	206	−3.5
4/27/37	100	2	156	212	0
5/ 2/37	100	3	156½	213	+1

There was marked diuresis. The patient was kept on courses of thyroprotein, 100 mg., q.d. for 3 weeks, with one week rest intervals until weighed 135 lb.

Case 13. Miss P.S., a 20-year-old female salesclerk, unmarried, height 63½ in., was markedly obese with a general fat distribution. She was lethargic. Menses were normal. Slight hypertrichosis. The patient would not stay on a diet. She had marked sweating while under treatment, slight increased diuresis was noted. There was no later follow-up.

Date	Thyroprotein, daily dose mg.	Duration weeks	Wt. lb.	O_2 Consumption cc.	B.M.R. %
10/20/36	No medication		203	271	+ 7
10/27/36	150	1	198½	278	+10
11/ 5/36	150	2	197½	254	0
11/12/36	150	3[1]	202	274	+ 8
11/19/36	150	4	200½	263	+ 3

[1] Patient had a cold for past week, no fever, she forced fluids.

Case 14. J.G., a 21-year-old, unmarried nurse, height 62 in., was markedly overweight particularly with regard to thighs and buttocks. Periods were essentially normal and regular. Diabetes mellitus was suspected but a sugar tolerance test result was normal. An exogenous factor unquestionably played a role in the genesis of the obesity. She had lost 6 lb. in 3 weeks of dieting alone. Her. B.M.R. 6 months previously had been +21%.

Date	Thyroprotein, daily dose mg.	Duration weeks	Wt. lb.	O_2 Consumption cc.	B.M.R. %
9/ 8/36	No medication		206	287	+17
9/20/36	6 tablets	2	201	270	+11
9/27/36	6 tablets	3	198	234	− 2

Case 15. Miss E.M., a 26-year-old stenographer, single, had exogenous obesity. Height was 61 in. She was on a 1,000-calorie diet while studied. There was marked sweating and diuresis from thyroid treatment, but no toxic symptoms or signs.

Date	Thyroprotein, daily dose mg.	Duration	Wt. lb.	O_2 Consumption cc.	B.M.R. %
5/10/36	No medication		168	260	+17
5/17/36	150	1 wk.	165	243	+10½
5/24/36	150	2 wk.	161½	234	+ 7
6/ 4/36	No medication	10 days	162		
6/18/36	150	14 days	159	230	+ 6

Abstracts of
CURRENT CLINICAL LITERATURE

Editor: HANS O. HATERIUS. *Collaborators:* E. B. ASTWOOD, ISRAEL BRAM, JOHN C. BURCH, JOHN C. DONALDSON, MURRAY B. GORDON, ARTHUR GROLLMAN, E. C. HAMBLEN, FRANK A. HARTMAN, R. G. HOSKINS, J. E. HOWARD, ALLAN T. KENYON, J. T. LEWIS, JOSEPH M. LOONEY, A. E. MEYER, C. C. PFEIFFER, GEORGE W. THORN, EMMERICH VON HAAM.

ADRENALS

ANONYMOUS.

Treatment of Addison's disease. *Lancet* 239: 200. 1940.

Treatment of severe Addison's disease with adrenal cortical extracts is very costly (up to $2,000 yearly). Synthetic desoxycorticosterone is much less expensive and now has been successfully used for 2 years. Implantation of pellets obviates the necessity for frequent injections. At the crisis all cases must receive cortical extract alone or the extract plus desoxycorticosterone, salt and glucose. Mild cases can be kept in good health by simply taking up to 20 gm. of extra NaCl daily and moderate cases maintained by pellet implantation or injection of the synthetic drug and added salt.—*J. B. Paton.*

FERREBEE, J. W., C. RAGAN, D. W. ATCHLEY AND R. F. LOEB.

A comparison of certain effects of desoxycorticosterone acetate, corticosterone and cortical extract on a patient with Addison's disease. *Endocrinology* 27: 360. 1940.

The effects of large doses of desoxycorticosterone acetate, corticosterone and cortical extract added to a maintenance dose of desoxycorticosterone acetete in a patient with Addison's disease were compared. Under the conditions of the study all 3 preparations had some effect upon the excretion of Na and K salts, most marked in the case of desoxycorticosterone acetate. None of the preparation had demonstrable effects upon protein metabolism as measured by N excretion. The effects of corticosterone and cortical extract upon the carbohydrate metabolism, over the time administered in this study, were not of a magnitude sufficient to be of practical value in the Addisonian patient regulated with desoxycorticosterone acetate.—*Authors' summary.*

FLORIS, M.

A study of the relation between vitamins and hormones. The effects on circulation of adrenal cortical hormone and of vitamin C in infectious states. *Ormoni, Turin* 2: 849. 1940.

Eight patients with infectious disease and hypotonia responded well to cevitamic acid and to extracts of adrenal cortex. The 2 agents have analogous anti-shock actions, and were more effective when administered together.—*G.A.E.*

GILMAN, A.

Use of cortical extract to promote excretion of bromides. *J.A.M.A.* 116: 889. 1941.

In a letter to the editor Gilman points out that the observations of Bondurant and Campbell on the use of cortical extract to promote bromide excretion is contrary to the theory of action of cortical hormone. The data on serum chloride varied 300% which Gilman says is unusual. More convincing chemical data are necessary before this method can be advocated.—*C.P.*

HARRISON, F. G., AND H. H. POTE.

Post-operative adrenal insufficiency. *J. Urology* 45: 322. 1941.

This is a detailed case report. In removing a badly damaged kidney, the right adrenal was injured. Acute insufficiency developed within an hour. Prompt treatment with sodium chloride and cortical extract tided the patient over the crisis. He was discharged cured a month later and was well and working a year and a quarter afterward.—*J.C.D.*

HJORT, A. M., E. J. DEBEER AND L. O. RANDALL

Experiences with the biological assay of several sympathicotonic substances including epinephrine. *J. Pharmacol. & Exper. Therap.* 71: 105. 1941.

Statistical methods are applied to the bioassay of epinephrin and other sympathicotonic substances. These studies indicate that linear dose-response relationships exist only in portions of the selected data and not for the whole range of data. The authors' statistical approach may serve to accentuate qualitative differences in drug action.—*C.P.*

MARKS, T. M., J. M. THOMAS AND J. WARKANY.

Adreno-cortical obesity in children. *Am. J. Dis. Child.* 60: 923. 1940.

One case of adreno-cortical obesity in a 10½ month old ♀ is described and 24 cases from the literature are reviewed. The obesity may commence at any age, more often in ♀ ♀, the ratio being 7:1, and is characterized by a so-called buffalo type of obesity not necessarily accompanied by gigantism. Abnormalities of the genitalia are not necessarily present. Hirsutism is perhaps the most constant finding, especially on face, trunk and pubic region. Acne is frequent even in very young children. Hypertension is a frequent symptom. Normal mental de-

velopment occurs, but as disease progresses the patient becomes listless, apathetic and dull. Blood findings are essentially normal. B.M.R. may be low. Tests of renal function give normal results. High values for urinary androgens are found. Means of differential diagnosis are indicated. Timely operation is the treatment of choice. Endocrine treatment has been tried.—*H.O.H.*

PERLA, D., AND J. MARMORSTON.

Suprarenal cortical hormone and salt in the treatment of pneumonia and other severe infections. *Endocrinology* 27: 367. 1940.

The value of parenterally administered suprarenal cortical hormone (together with salt and excess fluid by mouth) was demonstrated in a number of severe infections, including 17 cases of pneumonia, a case of induced malaria with periods of collapse and in severe grippal infections. The criterion of its value was noted in the maintenance of normal blood pressure, decrease in signs of toxicity, avoidance of circulatory collapse, maintenance of appetite and sense of well-being, decrease in the tendency to complications, absence of distention and shortening of convalescence.—*Authors' summary.*

ROGOFF, J. M., AND R. CORTELL.

Epinephrine output from the adrenal glands in experimental hyperthyroidism. *J. Lab. & Clin. Med.* 26: 981. 1941.

Six adult dogs received desiccated thyroid (0.5 gm. to 1.3 gm. per kg. of body weight) for periods ranging from 3 to 12 weeks. The response to thyroid extract was followed by determining the changes in pulse rate, body weight and B.M.R. At the end of the period of thyroid feeding the animals were killed for determinations of the rate of liberation of epinephrin from the adrenals by the method of Stewart and Rogoff in which adrenal vein blood is obtained at a known rate of flow via the 'cava pocket' and the epinephrin concentration in the blood is determined by its action on rabbits' intestinal segment. Ether anesthesia was employed for the operative procedures. The experiments indicated that thyroid feeding induced no detectable change in the rate of liberation of epinephrin. The output was within the same range as was noted in normal, control animals.—*G.W.T.*

ROGOFF, J. M., G. N. STEWART AND R. CORTELL.

Epinephrine secretion from the adrenal glands in relation to parathyroid activity. *J. Lab. & Clin. Med.* 26: 1084. 1941.

Thyroparathyroidectomy was performed on 11 dogs and 11 cats and subsequently quantitative determinations of the rate of liberation of epinephrin from the adrenals was made 2 to 50 days following operation by the method of Stewart and Rogoff. None of the thyroparathyroidectomized cats showed significant alteration in the rate of liberation of epinephrin from the adrenals. Among the dogs, however, a definite reduction in epinephrin output was noted in 3. Ten dogs were treated with parathyroid extract (30–300 U. daily) for 1 to 14 days. In all cases treatment was followed by a marked elevation in blood Ca level. In only 1 animal was the rate of liberation of epinephrin from the adrenals found to be outside the range ordinarily observed in normal animals.—*G.W.T.*

ROWNTREE, L. G.

The results of various forms of treatment of Addison's disease. *Med. Clin. N. A.* 24: 1779. 1941.

This is a general review of the subject with a clinical description of a case of Addison's disease in a white ♂, age 21, with gynecomastia. He has been followed up for a period of over 2 years through various methods of treatment. He has done well and probably will continue to do well under an adequate supply of cortical hormone. Also salt therapy has contributed much to his welfare, since its use has permitted a reduction in dosage of the cortical hormone. The patient is still pigmented, though the administration of adrenalin to the point of tolerance has reduced pigmentation considerably. The modern treatment of Addison's disease results in rehabilitation and increases longevity.—*I.B.*

RUSHTON, J. G., R. W. CRAIG, AND L. K. STALKER.

Spontaneous hypoglycemia due to atrophy of the adrenal glands. *Arch. Int. Med.* 66: 531. 1940.

A case is described of a young woman suffering from spontaneous attacks of hypoglycemia. At operation no tumor of the pancreas was revealed, nor could any other cause be found. Postmortem examination revealed extreme atrophy of both adrenal glands, and this is considered the cause of the hypoglycemia. Another finding possibly contributory was extensive inflammatory destruction of the thyroid, of the type described by Hashimoto.—*Authors' summary.*

SUDDS, MARJORIE V. N.

The cell contents of the cortex of the suprarenal gland. *Endocrinology* 26: 895. 1940.

Discrete fuchsinophil granules were found in 24% of adult ♂ suprarenals and in 28% of the ♀ suprarenals examined. The % of glands containing granules increased with age. With the exception of the gland of a 16-week-old fetus, granules were not found in any case under 24 years.—*F. H. Snyder.*

THORN, G. W., R. P. HOWARD AND H. DAYMAN.

Electrolyte changes in pulmonary tuberculosis. With special reference to adrenal cortical function. *Bull. Johns Hopkins Hosp.* 67: 345. 1940.

Determinations of blood serum concentrations of NaCl, K, CO_2-combining power and plasma volume in patients with tuberculosis showed a striking decrease in serum Cl concentration, compensated in part by an increase in serum HCO_3 concentrations. NaCl deprivation tests resulted in marked reduction in serum Cl concentrations, a decrease not accompanied by a decrease of corresponding magnitude in serum Na. During the 3rd day of test, although concentrations of Na and Cl in urine were within normal limits, the concentration of Cl exceeded that of Na. The increase in Cl excretion did not approach in magnitude the increased excretion observed in adrenal cortical deficiency. Moreover, the alteration in Cl metab-

olism was not associated with a corresponding change in Na metabolism. Patients with tuberculosis differed from patients with Addison's disease in ability to maintain a normal serum concentration of Na and K, to preserve total blood volume, and to withstand a regimen of NaCl deprivation with supplementary K medication without manifesting the changes in body weight, blood pressure and urinary concentration of Na and Cl typically observed in presence of adrenal cortical deficiency. In absence of acidosis or renal disease the response to the Cutler, Power and Wilder NaCl deprivation test is of great aid in differentiating patients with tuberculosis from patients in whom tuberculosis is complicated by adrenal cortical or anterior pituitary deficiency.—*From authors' summary.*

THORN, G. W., G. F. KOEPF, R. A. LEWIS AND ELIZABETH F. OLSEN.

Carbohydrate metabolism in Addison's disease. *J. Clin. Investigation* 19: 813. 1940.

Some or all of the following abnormalities in carbohydrate metabolism were observed in a large proportion of patients with Addison's disease: 1) a low-normal fasting blood glucose level, 2) striking hypoglycemia, following either a 24-hour fast, oral or i.v. administration of glucose, or during fevers or infections, and on a high-fat, low-carbohydrate diet, 3) decreased threshold at which hypoglycemic symptoms appeared, 4) flat type of oral glucose curve, 5) absence of rebound in blood glucose following administration of i.v. glucose, 6) decreased glycemic response to insulin, 7) high standard R.Q., 8) increase over normal in R.Q. following glucose administration, 9) low-normal B.M.R. Desoxycorticosterone acetate therapy failed to alter the abnormalities. Large quantities of adrenal cortical extract alleviated the condition. It is suggested the adrenal cortical hormone has a direct action on carbohydrate metabolism in man, in that cortical hormone increases ability of organism to form glucose and glycogen from intermediate products of both carbohydrate and protein metabolism and in this manner regulates the utilization of carbohydrate.—*From authors' summary.*

TURNOFF, D., AND L. G. ROWNTREE.

Successful sublingual therapy in Addison's disease. *J.A.M.A.* 116: 2016. 1941.

Confirmation is given, with 2 case histories, of Haymaker's observation that desoxycorticosterone acetate in propylene glycol is an effective sublingual form of therapy in Addison's disease.—*C.P.*

WILLSON, D. M., E. H. RYNEARSON AND T. J. DRY.

Cardiac failure following treatment with desoxycorticosterone acetate. *Proc. Staff Meet. Mayo Clin.* 16: 168. 1941.

The report on a woman aged 33 suffering from Addison's disease is given. The use of diets low in K (3 gm.) and high in Na (10 gm. NaCl, 5 of Na citrate) caused relief of symptoms. Subsequently desoxycorticosterone, 5 mg. daily, was given and the patient returned home. Two months later she returned in severe prostration and gave a history of diarrhea, nausea and anorexia. Examination revealed edema of ankles and engorgement of veins of neck and arms and a high venous pressure (15 cm. of water). The heart showed enlargement by x-ray and there was a loud systolic murmur. The serum K was 14.0 mg. and the Na 324 mg. per 100 cc. A diagnosis of acute myocardial failure was made and the intake of Na was restricted, extra K was given and 500 cc. of blood removed by venesection. The patient recovered and was maintained on 3 mg. of desoxycorticosterone acetate, 4 gm. K and 8 gm. of NaCl daily. The differential diagnosis between the crisis of Addison's disease and overdosage with desoxycorticosterone acetate is given. The determination of the venous pressure is the most important single test. This is high in overdosage, and low in Addisonian crises. —*J.M.L.*

ENDOCRINE GENERAL

BRUCH, H.

Obesity in childhood and endocrine treatment. *J. Pediat.* 18: 37, 1941.

The author states that the diagnosis of an endocrine disorder in an obese child and long continued glandular treatment are not only unjustified but harmful, in so far as they produce or increase the apprehensive and over solicitous attitude of the parents and block the road for a rational treatment of the obesity. Two cases are reported; one in a boy of 6 in whom obesity developed while receiving gonadotropic hormone and another in a girl of 11 who grew obese after a thyroid enlargement had developed.—*M.B.G.*

COMFORT, M. W., AND A. E. OSTERBERG.

Pancreatic secretion in man after stimulation with secretin and acetylcholine chloride. *Arch. Int. Med.* 66: 688. 1940.

Secretin and mecholyl chloride produced contrasting effects on pancreatic secretion, the former producing a large volume of duodenal contents, increasing the pH values and effecting a prolonged reduction in the concentration of enzymes. Mecholyl chloride increased volume only slightly, did not appreciably affect the pH values, and provoked a prolonged increase in the concentration of enzymes.—*From authors' summary.*

EDITORIAL.

Non-endocrine therapy of endocrine disorders. *J.A.M.A.* 116: 596. 1941.

This editorial comments on the increasing use of non-endocrine products to relieve symptoms of glandular imbalance or insufficiency. Examples given are sodium chloride in Addison's disease and ammonium chloride in premenstrual distress or tension.—C.P.

GREENLEE, D. P., J. G. LLOYD, A. J. BRUECKNER AND W. S. MCELLROY.

Adenoma of the islets of Langerhans, with hyperinsulinism, associated with adenoma of the thyroid. *Ann. Surg.* 112: 378. 1940.

A case is reported of hyperfunction in both an adenomatous goiter and in an adenoma of the islets of Langer-

hans, with low blood sugar and high B.M.R., in which both conditions were corrected by suitable surgical therapy. Biologic assays of the pancreatic tumor tissue proved its insulin activity. Most important clinical feature of hyperinsulinism were the attacks of coma or unconsciousness which appeared after patient abstained from food for some time, or following bouts of exercise, a condition which was relieved by administration of sugar. —*From authors' abstract.*

HUGHES, E. C.

Relationship of the thyroid and adrenal glands to the toxemias of pregnancy. *Am. J. Obst. & Gynec.* 40: 48. 1940.

Pregnancy has an effect on the glands controlling metabolism, in the 1st and 3rd trimesters. Administration of thyroid to those with low rates in the 1st trimester reduces the incidence of late toxemias 50%. Serum Na is lowered during toxemias, but is constant throughout normal pregnancy. Injection of early and late toxic urine into virgin rabbits produces thyroid and adrenal lesions and pathological changes in the liver and kidneys typical of early and late toxemias of pregnancy. These changes may be due to hormonal imbalance or overproduction of some toxic metabolite, or both.—*Chemical Abstracts.*

LIU, S. H., H. I. CHU, H. C. HSU, H. C. CHAO AND S. H. CHEU.

Calcium and phosphorus metabolism and osteomalacia. XI. The pathogenetic role of pregnancy and relative importance of calcium and vitamin D supply. *J. Clin. Investigation* 20:255. 1941.

Ca, P and N balance studies were made on 10 Chinese women admitted during various stages of pregnancy. The subjects were divided into 3 groups: I. 3 normal controls, there being no evidence of tetany or x-ray evidence of osteomalacia; II. 4 subjects with mild osteoporsis, 3 of whom had active tetany prior to the metabolic studies; III. 3 subjects with advanced osteomalacia, marked skeletal rarefaction, deformity and fractures. A comparison of the metabolic behavior during pregnancy of patients with severe or mild osteomalacia with that of subjects showing no skeletal lesions revealed no essential differences. With adequate vitamin D supply and moderately high intake of Ca and P, subjects with various skeletal conditions had no difficulty in retaining amounts of the minerals sufficient for the needs of gestation. In fact, under similar regimen, osteomalacic patients tend to retain more Ca and P in an attempt to replenish the depleted mineral store as well as to provide for fetal growth. Furthermore, in contrast to lactation, where the physiological activity is such that mineral requirement has to be increased much above the quantity which is secreted in the milk even in the presence of adequate vitamin D, there is no such factor in pregnancy. While high Ca intake tends to ameliorate the effects of vitamin D deficiency, the latter conserves Ca. Of the two, vitamin D is probably more important provided a reasonable level of Ca intake is available.—*G.W.T.*

RADNER, S.

On Lawrence-Moon-Biedl's syndrome. *Acta med. Scandinav.* 105: 141. 1940.

A description is given of 2 sisters suffering from this syndrome showing the complete picture of retinitis pigmentosa, dystrophia adiposogenitalis, oligophrenia and polyor syndactylia. The hereditary nature of the condition is questioned as no other cases were found in 4 generations. It was proved by means of approximate calculations that the syndrome can hardly be due to a random combination of symptoms.—*J.M.L.*

SCICLOUNOV, F., AND E. MARTIN.

Modification of induced hyperglycemia by ingestion of fat. *Presse med.* 48: 691. 1940.

Ingestion of fat has no influence on the blood sugar in the healthy individual. The hyperglycemia caused by a mixture of sugar and fat shows a flat and often variably oscillating curve as compared with that caused by sugar alone. It is assumed that fat interferes with the intestinal absorption of sugar.—*A.E.M.*

SELYE, H.

On the role of the liver in the detoxification of steroid hormones and artificial estrogens. *J. Pharmacol. & Exper. Therap.* 71: 236. 1941.

The anesthetic and toxic effect of desoxycorticosterone acetate, progesterone, testosterone benzoate, estradiol, and stilbesterol are greatly increased in partially hepatectomized animals. The author reasons that since this operation does not prolong ether anesthesia, it would appear that the liver is the site at which all of the above compounds are detoxified.—*C.P.*

TALBOTT, J. H., F. S. COOMBS, W. V. CONSOLAZIO AND L. J. PECORA.

Diabetes insipidus associated with diabetes mellitus. Metabolic studies and report of a case. *Arch. Int. Med.* 66: 607. 1940.

Metabolic studies on a patient with diabetes mellitus and diabetes insipidus are described, the clinical diagnosis of both dyscrasias apparently being confirmed by the laboratory data. The inference of a hyperplastic and hyperfunctioning anterior pituitary lobe encroaching upon the supra-optico-hypophyseal pathway gained support from roentgen examination. Chronologically the symptoms of diabetes mellitus preceded those of diabetes insipidus. Serum Na and Cl concentrations were found increased on many occasions. Renal function tests resulted in values within the normal range, except for those for Na and Cl.—*From authors' summary.*

TSUJI, K.

Four cases of a new type of pluriglandular insufficiency. *Acta Scholae Med. Univ. Imp. Kioto.* 23: 200. 1939.

Symptoms and results indicated pluriglandular insufficiency in 4 cases reported, although final confirmation by autopsy was not possible. There was evidence of hypofunction of thyroid, hypophysis and parathyroids. Thyroid size was greatly diminished, and it was felt that this

accounted for the arteriosus, hypotrichosis, scleroderma and skin pigmentation. Despite this, metabolism was increased, as evidenced by increased secretion of urinary N and creatine, lowering of blood sugar level and epinephrin glycosuria. These apparently contradictory symptoms give evidence of hypofunction of the parathyroids, which are considered to function antagonistically to the thyroid. Signs of such hypofunction appeared as Chvostek's sign, cataract formation and increase in the ratio of ammonia N to urinary N. Moreover, disturbances found in tooth development indicated hypofunction of thyroid and parathyroid glands. X-ray examination of hypophysis in 3 cases revealed atrophy. Symptomatically this atrophy found expression in abnormally rich fatty accumulations on breasts and in the gluteal region, with emaciation of peripheral parts of extremities, acromicria and hypogenitalism. Evidences of vagotonia were attributed to hypofunction of the thyroid. Deficient body growth was attributed to thyroid and hypophyseal hypofunction. The essential pluriglandular disturbances in all 4 cases appeared in childhood, becoming greatly emphasized at approach of puberty.—*H.O.H.*

WAISMAN, M., AND E. J. KEPLER.

Alopecia areata. *J.A.M.A.* 116: 2004. 1941.

Because changes in hair growth accompany many endocrine deficiencies, it has been thought that alopecia could generally be ascribed to endocrine deficiency. The authors survey of a total of 138 cases and give the sex and age incidence. They conclude that there is no definite endocrine abnormality associated with alopecia. The instances in which concomitant features of definite endocrine disease occur are relatively few, and these associations appear to be incidental rather than causal.—*C.P.*

WEINBERGER, L. M., AND F. C. GRANT.

Precocious puberty and tumors of the hypothalamus. *Arch. Int. Med.* 67: 762. 1941.

This valuable paper consists essentially of the report of a case in detail, a review of the literature and a pathophysiological explanation of the precocious sexual syndrome. The case described is a boy 7 years 11 months old. The authors suggest that precocious puberty may be a purely hypothalamic syndrome, particularly the posterior portion of the hypothalamus. This contribution does not lend itself to abstracting but must be studied in its entirety.—*I.B.*

WERNER, S. C.

A quantitative study of the urinary excretion of hypophyseal gonadotropin, estrogen, and androgen of normal women. *J. Clin. Investigation* 20: 21. 1941.

Data are presented on the gonadotropin, estrogen and 'androgen' content of the urine of 5 normal women with regular menstrual cycles over a period of 3 to 4 months for each woman. The procedure of Levin and Tyndale was followed for gonadotropin. Estrogen and 'androgen' were quantitatively recovered from the supernatant and the alcohol-acetone-ether washings of the tannic acid precipitate. Estrogen was assayed by the Kahnt-Doisy procedure and 'androgen' (17-ketosteroid) was determined by the Zimmerman reaction (Callow and Callow). The general pattern of hormone excretion was similar in 4 of the 5 subjects, i.e., a more or less constant 17-ketosteroid excretion, a central peak of gonadotropin and estrogen excretion, followed by a second peak of estrogen output. However, the pattern was not exactly reduplicated from cycle to cycle in the same individual. The relation between the peaks of estrogen and gonadotropin was not constant. Gonadotropin was demonstrable throughout the cycles of all but one subject. The relative constancy of output of 17-ketosteroid makes it possible to define the limits of normal secretion of this substance. The variation in patterns of excretion of gonadotropin and estrogen in different cycles makes the determination of the range of normality of these much more difficult.—*G.W.T.*

GONADS

ABARBANEL, A. R., AND M. D. KLEIN.

Clinical experiences with stilbestrol. *N. Y. State J. Med.* 41: 383. 1941.

A group of patients was given stilbestrol in doses of 50 to 1,000 mg. orally 1 to 11 days postpartum, the babies being allowed to nurse. In all cases lactation was adequately established provided nursing continued, although appearance of the normal average amount of milk secretion was delayed for 2 to 7 days after the last dose. Administration in another group indicated that the drug in doses of 50 to 500 mg. orally had no effect on established lactation. In an attempt to induce labor stilbestrol in doses of 100 to 200 mg. acted as a priming agent for the uterus in a large % of cases where one or more previous medical inductions had failed. Used alone, stilbestrol did not induce labor. A series of 75 cases was treated in which simpler barbiturates and bromide drugs had proved unsuccessful in treatment of the menopausal syndrome. With dosages of 0.1 mg. once or twice daily, increased if necessary, uniformly good results were obtained. Pellets of 15 mg. of crystalline stilbestrol were employed in a series of cases in which oral administration had proved beneficial. Inserted subcutaneously in the thigh, these were effective for 2 to 3 months. Stilbestrol in the form of an ointment was found beneficial in senile vulvovaginitis and also in treatment of gonorrheal vulvovaginitis in children. No ill effects followed doses as high as 250 mg. daily to 1,500 mg. per week. The patients might complain of nausea, emesis or gastrointestinal upsets, but these could be greatly controlled by the concomitant administration of small doses of bile salts.—*A. Levitt.*

ALLAN, F. N.

The treatment of menopausal symptoms with stilbestrol. *The Lahey Clinic Bulletin* 1: 14. 1940.

A report of results in 32 cases. In 6 the menopause was artificially induced; in the remainder it occurred spontaneously. In 10 of the cases nausea, mild abdominal discomfort and malaise resulted and in 3, vomiting occurred in addition. In all but 2 cases reduction of hot flashes and relief from nervous symptoms was obtained. In 21 the results were unquestionably good to excellent. In 5 of the artificial-menopause cases in which the symptoms were

severe and rather intractable, results were particularly gratifying. The material proved effective by mouth, by injections and by inunctions. One mg. daily usually sufficed.—*R.G.H.*

ALLEN, E.

Glandular physiology and therapy. Physiology of the ovaries. *J.A.M.A.* 116: 405. 1941.

Allen summarizes the extensive literature (97 references) on the physiology of the ovaries as it appears in the lower mammals.—*C.P.*

BACHMAN, C., D. LEEKLEY AND H. HIRSCHMANN.

Excretion of sodium pregnandiol glucuronidate in urine of normal human pregnancy. *J. Clin. Investigation* 19: 801. 1940.

The urinary excretion of Na pregnandiol glucuronidate was studied by the method of Venning in 6 cases of normal pregnancy at weekly intervals from the 3rd month to full term. Results confirmed the general findings of Venning, Henry and Browne with respect to the normal gestational ranges and levels of the excretion but showed in addition that the excretion curve is characterized by cyclic monthly fluctuations and by a peak during the last month. At the time of labor the rate of excretion is falling. Additional data from 5 cases of multiple pregnancy indicated that the ranges and levels of excretion are not markedly different from single-fetus gestations. It is suggested the rate of excretion during normal pregnancy is determined by the maturity of gestation rather than by the size or number of fetuses and placentas.—*Authors' summary.*

BARAHAL, H. S.

Testosterone in psychotic male homosexuals. *Psychiatric Quart.* 14: 319. 1940.

There is considerable controversy as to whether homosexuality represents a constitutional, endocrinological disturbance or whether it is primarily of psychogenic origin. Seven psychotic ♂ overt homosexuals were given large doses of testosterone propionate over an extended period of time. Most of them showed the effects of stimulation of the secondary sex characters, particularly in an increased growth of hair and the change of a feminine pubic hair line to a more masculine type. Along with these, there was generally an increase in their homosexual practices. This study would tend to indicate that homosexuality is not primarily an endocrinological disturbance, and that the hormone determines the degree of libido rather than its direction.—*Author's abstract.*

BARTELMEZ, G. W.

Glandular physiology and therapy. Menstruation. *J.A.M.A.* 116: 702. 1941.

Bartelmez summarizes the present knowledge of the menstrual cycle. Three types of mammalian bleeding are menstruation, implantation bleeding (placental sign) of Long and Evans and preovulatory bleeding associated with hyperemia. The menstrual cycle is divided into 6 phases—the postmenstrual phase of inactivity, the primary growth phase, secondary growth phase, phase of involution, phase of bleeding and phase of repair. The mechanism of menstruation is also discussed.—*C.P.*

CARMICHAEL, H. T., AND W. J. NOONAN.

The effects of testosterone propionate in impotence. *Am. J. Psychiat.* 97: 919. 1941.

Testosterone propionate was given in dosage of 25 mg. 3 times a week to 18 impotent men. Careful examinations had revealed no anatomical or endocrine abnormality in 17 of the cases. In some of the patients it was apparent that psychological factors were operative in causing the incapacity and may have played a part in all. In 7 of the cases relief of the impotence was secured; in 11, not. It seemed probable that the injections in the successful cases were effective largely or wholly because of their psychological effect since substitution of placebos caused no loss of potency and it persisted after the injections were discontinued. The possibility is pointed out that initial physiological stimulation might in some cases have so reassured the patients as to have corrected their psychic impotence. Contrariwise, in those suffering from sex conflicts the stimulation may have so increased their anxieties as to have further confirmed their disability.—*R.G.H.*

CORNER, G. W.

Glandular physiology and therapy. Corpus luteum hormone. *J.A.M.A.* 116: 591. 1941.

The literature on the corpus luteum hormone (progesterone) is reviewed under the following headings: action on the uterine mucosa and muscle; progesterone—the international unit and method of assay and pregnandiol; the clinical possibilities of therapy of recurrent abortion; threatened abortion, dysmenorrhea, after-pains, metorrhagia, menorrhagia, amenorrhea, and other conditions.—*C.P.*

DANIELS, G. E., AND E. S. TAUBER.

A dynamic approach to the study of replacement therapy in cases of castration. *Am. J. Psychiat.* 97: 905. 1941.

Effects of testosterone propionate on the personality manifestations and the sexual activity of two castrates are reported. The study was controlled with estrogen and oil-blank placebos. It appeared that the administration of androgen rather regularly caused florid dreaming and less regularly increased erotic activity. The objective sexual behavior was found to be influenced both by the giving or withholding of androgen and by environmental circumstances (the transference situation and intercurrent illness of wife). It was concluded that in the practical treatment of hypogonadism both psychotherapy and replacement therapy may be desirable. The study of the dream material as influenced by the hormone treatment offers a new approach to the study of dream symbolism.—*R.G.H.*

DODDS, E. C.

The new estrogens. *Edinburgh M. J.* 48: 1. 1941.

This is a brief and informative history of our knowledge of these compounds. Special note is made of the relative toxicity of stilbestrol and its modifications. In 252 patients

treated with stilbestrol dipropionate 1.3% showed toxic symptoms. This is about the same percentage as would be found if stilbestrol were used and about 5 times the percentage showing toxic symptoms with hexosterol. Untoward effects with these drugs are not serious, they tend to wear off with continued treatment and are more prevalent with high doses. Some patients show a distinct idiosyncrasy to these drugs.—*J.C.D.*

DOISY, E. A.

Glandular physiology and therapy. The estrogenic substances. *J.A.M.A.* 116: 501. 1941.

The estrogenic substances are reviewed under the following headings: chemistry; biological reactions which are subdivided into uterine, tubal, mammary, the anterior pituitary, effects; the effect on calcium in fowls; the bioassay and metabolism of estrogens; estrogenic therapy.—*C.P.*

DOUGLAS, R. J.

The male climacteric: its diagnosis and treatment. *J. Urology* 45: 404. 1941.

Fifty-eight men suffering from a general decrease in mental and physical powers were carefully studied. In 30 of these the changes were not due to outside factors or pathological conditions but to physiological alterations within the body. On the basis of these cases, which varied in age from 42 to 57 years, the author concludes. "There is a transitional phase of adult ♂ life which may be likened to the climacteric of the ♀, occurring in the middle or late forties. In those cases a diagnosis of the climacteric is based on urinary disturbances, bladder neck malfunction, fatigue, indecision, hot flashes, and nocturnal diaphoresis, decreased libido, impending impotence, and some degree of prostatic involvement. In those where no abnormality exists, the gonadal substance may be stimulated to greater secretion and activity following the use of testosterone propionate in doses as small as 30 mg. The diagnosis of a transitional phase in ♂ adult life and its treatment is evidence that testosterone propionate is a valued addition to our armamentarium."—*J.C.D.*

FLUHMAN, C. F.

Glandular physiology and therapy. Ovarian dysfunctions and their treatment. *J.A.M.A.* 116: 831. 1941.

The ovarian dysfunctions are reviewed and the following syndromes are discussed: pubertas praecox; pseudopubertas praecox; delayed menarche and primary amenorrhea; secondary amenorrhea; polymenorrhea and oligomenorrhea; hypomenorrhea and hypermenorrhea (menorrhagia); anovulatory menstruation; metropathia haemorrhagia; total absence of ovarian function; premenstrual tension; intrinsic dysmenorrhea. The therapy of intrinsic dysmenorrhea is outlined and the author warns that inclusion of dysmenorrhea in his article is made for purposes of convenience and does not necessarily indicate that he believes dysmenorrhea is due to ovarian dysfunction.—*C.P.*

GESSLER, G.

The influence of folliculin injections on the glycemia in women past menopause. *Presse med.* 48: 780. 1940.

High doses of estradiol benzoate (50,000 U) were given to 4 women past menopause having diabetes. In 2 the diabetes dated from onset of menopausal symptoms. These 2 responded to treatment with a considerable reduction of the fasting blood sugar which effect lasted for several days after cessation of the injections. The other 2 had diabetes of longer standing; they were not affected by the estrin treatment. It is supposed that the first 2 cases were of pituitary type diabetes that responded to the depressing action of estrin. It is mentioned that the same dose of estrin depressed the metabolic rate in a case of postmenopausal hyperthyroidism.—*A.E.M.*

GRAY, L. A., AND J. D. GORDINIER.

The effect of diethylstilbestrol and diethylstilbestrol dipropionate on postmenopausal vaginitis and symptoms. *Am. J. Obst. & Gynec.* 41: 326. 1941.

One hundred and eleven women were treated. Route of administration of the drugs was intramuscular or as plain or enteric coated tablets by mouth. Dosage varied from 0.5 to 5 mg. daily or as infrequently as 2 weeks. Of the 108 patients with menopausal symptoms, 47% had 4+ improvement, 24% 3+ improvement, 11% 2+ to 1+ improvement and 18% did not improve. Of the 97 patients with atrophic vaginal changes, 73% showed 4+ improvement, 20% 3+ improvement, 7% 2+ to 1+ improvement and 3% did not improve. Postmenopausal bleeding occurred in 12 of the patients treated. Nausea and vomiting occurred in 25% of the patients who received oral administration; however, only 1 of the 33 patients who received enteric coated tablets of the drug had these symptoms. The authors conclude that the results obtained from the treatments compare favorably with those from natural estrogens and that enteric coating decreases the undesired gastrointestinal side effects.—*E.C.H.*

GREENE, R. R.

Endocrine therapy for gynecologic disorders. *Med. Clin. N. A.* 25: 155. 1941.

This is an excellent review and tabulation of hormones for gynecologic conditions. In general, sex hormones should be given by intramuscular route as the estrogens lose much of their potency if given orally. For oral administration estradiol is the estrogen of choice; the benzoate and the dipropionate are the most effective. Progesterone is ineffective by mouth and must be given in doses higher than commonly recommended. Testosterone propionate is an efficient androgen when given intramuscularly but is valueless when given by mouth. Inunction of sex hormones has little practical value. Gonadotropic hormones are destroyed by the digestive enzymes and must be administered parenterally. Chorionic gonadotropin does not stimulate the human ovary and is of doubtful efficacy in the female. Equine gonadotropin stimulates corpus luteum formation but is of doubtful value at pres-

ent in women with abnormal ovarian function. Because of the crudity and lack of potency, most workers have had poor results with gonadotropic extracts of the anterior pituitary.—*I.B.*

GREENHILL, J. P.

Recent advances in gynecologic endocrinology. *Illinois M.J.* 79: 61. 1941.

This is a brief practical summary of the subject. The author discusses testosterone propionate and its use in the ♀, voicing a note of caution because of the occasional transient symptoms of virilism following its use. Gonadotropic hormone from the PMS is also discussed, with mention of contraindications. Finally, stilbestrol is commented upon. It is relatively inexpensive and highly effective when taken by mouth.—*I.B.*

HENRIKSEN, E.

A clinicopathologic investigation of the causes of menometrorrhagia. *Am. J. Obst. & Gynec.* 41: 179. 1941.

The author analyzes the clinicopathologic findings in a series of 1,500 women between the ages of 20 and 40 whose complaints were primarily those of abnormal uterine bleeding. The organic as well as the functional causes of irregular bleeding are considered. The segregation of the basic etiologic factor in each case is stressed as a prerequisite to a rational therapeutic approach. The complicated status of investigative and therapeutic approaches to menstrual aberrations is blamed to a large degree upon misinterpretation of endometrial findings and the misapplication of terminology. The author admittedly has offered no new theories, presented no new classifications or advanced any new ideas of therapy.—*E.C.H.*

HILLS, R. G., AND J. A. WEINBERG

Influence of estrin on callous formation. *Bull. Johns Hopkins Hosp.* 68: 238. 1941.

Three patients with delayed union were treated with estrogenic hormone, following which there was an increased callous formation at the site of fracture. In 9 out of 13 cats and 6 of 7 dogs there was also earlier and more abundant callous formation at the site of experimental fracture following the injection of the large doses of estrogen.—*A.G.*

KAUNITZ, H., G. F. AUSTRIA, A. GONZALEZ, F. SALES AND J. N. CRUZ.

Influence of follicular hormone on vitamin A deficiency. *Acta Med. Philippina* 2: 205. 1940.

Taking the dark adaptation of the patient as the expression and measure of vitamin A tissue content, there is the suggestive observation that follicular hormone (Menformon, Roche-Organon) improves the dark adaptation. The mechanism of such improvement has not been clarified. On the basis, however, of previous studies on disturbance of biologic permeability, it is suggested that the favorable response of vitamin A deficiency (as shown by poor dark adaptation) to follicular hormone therapy is due to an improvement of the disturbed biologic permeability of the tissue cells, increasing their selective affinity for vitamin A.—*From an abstract by H. Kaunitz.*

LARDARO, H. H.

Clinical evaluation of stilbestrol in women with hypoplastic genitalia. *Am. J. Obst. & Gynec.* 41: 301. 1941.

Thirty patients, 28 of whom had hypoplastic uteri were treated with intramuscularly administered stilbestrol. The usual dosage was 5 mg. thrice weekly. The number of injections varied from 2 to 42 over an interval of 14 weeks. Only 5 of the 28 patients showed some temporary or permanent changes in uterine size or consistency. The majority of patients experienced undesired side actions from the therapy: these were chiefly gastrointestinal in nature and disappeared when therapy was discontinued.—*E.C.H.*

LIN, HAZEL AI-CH'UN.

The treatment of gonococcal vulvo-vaginitis by estrogenic suppositories. *Chinese M. J.* 58: 527. 1940.

Twenty-one cases were healed in 7 to 61 days with human PU extract.—*C. D. Stevens.*

MACLEOD, J., AND R. S. HOTCHKISS.

The effect of hyperpyrexia upon spermatozoa counts in men. *Endocrinology* 28: 780. 1941.

Elevation of body temperature in man in conjunction with a simultaneous elevation of environmental temperature resulted in a marked drop in spermatozoa production. The effect of hyperpyrexia upon spermatogenesis did not become apparent for nearly 3 weeks and often lasted for a period of 50 days. The clinical inferences are discussed.—*From authors' conclusions.*

MAZER, C., S. L. ISRAEL AND E. RAVETZ.

The synthetic estrogen stilbestrol. An experimental and clinical evaluation. *J.A.M.A.* 116: 675. 1941.

After a single hypodermic dose of stilbestrol the estrogen output in the urine was elevated for only 5 days while with small oral doses a plateau of excretion was attained which lasted for at least 6 days. It was used effectively in migraine, vulvovaginitis, amenorrhea, menopausal syndrome, suppression of lactation and diabetes complicating the menopause. Extensive clinical data are presented to determine any biochemical changes induced by treatment in 189 patients. The toxic symptoms were sufficiently severe to warrant discontinuation of treatment in 42 patients (22%). At the recommended dosage level of 0.5 mg. daily the incidence of nausea and vomiting is only 3%.—*C.P.*

MOORE, C. R.

Physiology of the testis. *J.A.M.A.* 116: 1638. 1941.

In this review article the testis is discussed under the following headings: Spermatogenic activity and its variation in the animal kingdom; Pituitary and non-pituitary factors influencing spermatogensis; Internal secretory activity with methods of detection and isolation of the hormone; The periods of hormone secretion with modifying factors; The physiological effects of testis hormone.—*C.P.*

MUCKLE, C. W.

The suppression of lactation by stilbestrol. *Pennsylvania M.J.* 44: 305. 1940.

Stilbestrol was administered to 208 puerperal women for the purpose of inhibiting or suppressing lactation. Four dosage schedules were studied. It was found that 5 mg. doses were more effective than 1 mg. doses, and that the administration of a large dose within a short time gave better results than lengthening the period of administration. The optimum method is to administer 5 mg. 3 times a day for a total of 6 doses. Marked suppression of lactation occurred in 85% of patients, partial suppression in 13%, and no beneficial effect was noted in 2%. In 37% of 107 patients followed, there was a secondary recurrence of lactation. This was usually painless, slight in amount, and responded to further medication. Toxic effects, consisting chiefly of nausea, were noted occasionally. No major or permanent ill effects were noted. The use of stilbestrol is an efficient, useful, and safe method of suppressing lactation early in the puerperium.—*I.B.*

MUSSIO-FOURNIER, J. C., AND A. ALBRIEUX.

Absorption of sex hormones through the skin. A case of facial hypertrichosis improved by intradermal injections of folliculin. *Presse med.* 48: 569. 1940.

Male and female sex hormones applied to the skin in form of ointments or as solutions in oil or alcohol are well absorbed and therapeutically efficacious. Preferred local action may be obtained by application to the sensitive organ. In a case of facial hypertrichosis intradermal injections of folliculin produced considerable improvement in the corresponding area.—*A.E.M.*

NOTKIN, J., B. DENNES AND V. HUDDART.

Folliculin menformon (theelin) treatment of involutional melancholia. *Psychiat. Quart.* 14: 157. 1940.

Fifteen women suffering from involutional melancholia were treated with large quantities of ♀ sex hormone intramuscularly and orally for a period of 3 months. Nine of them showed slight improvement during the course of treatment. At the end 6 patients relapsed. Two others who failed to respond during the greater part of the treatment improved slightly toward the end of the therapy. Three months after termination of the treatment 3 patients were still maintaining mild improvement while 2 others relapsed. One patient began to improve at about this time. In no case was improvement of a sufficient degree to enable any of them to resume life outside the hospital. At a recheck 3 years later every patient who showed some improvement at one time or other was definitely worse. Three patients had transitory uterine bleeding during or after the course of treatment. No definite changes in the physical condition were observed as a result of the treatment. The prepsychotic personality, the individual's age and duration of the psychosis had no bearing upon the outcome of the treatment. In a control group of 10 patients who were given physiologic salt solution intramuscularly, only, under identical conditions, one patient had a mild and short-lived period of improvement. —*Authors' abstract.*

NOVAK, E.

Glandular physiology and therapy. Ovarian tumors of endocrine nature. *J.A.M.A.* 116: 947. 1941.

The ovarian tumors with a demonstrable hormonal activity are the granulosa called carcinoma, thecoma, luteoma, arrhenoblastoma, adrenal ovarian tumors and the struma ovarii or thyroid tumor of the ovary. The clinical effects of these tumors in children, and on women in the menacme, and postmenopausal life are discussed. —*C.P.*

PADDOCK, R.

A test for pregnancy, technic and comparative results. *South. M. J.* 34: 174. 1941.

The test is based on the fact that in active estrus the membrane closing the vagina in guinea pigs disappears. Three guinea pigs are used. The pectoral region is injected with 1.2 to 1.5 cc. of suspected blood serum. The animals are examined 24 and 48 hours later. Disappearance of the vaginal membrane is a positive result. With 3 animals there is only 1 chance in 416 that all will be in normal estrus at the same time. After a few days rest the animal can be used over again. Several were used 95 times in the 254 experiments reported. The results agreed with the Friedmann tests in all but 24 cases. There were no false positives. The simplicity of the procedure is emphasized. —*J.C.D.*

ROELSEN, E.

Attempts at treatment of eunuchoidism with gonadotropic hormone and testicular hormone. *Ugesk. f. laeger* 102: 123. 1940.

A sexually very retarded 23-year-old eunuchoid had puberty induced by heavy treatment with gonadotropic hormone. Testosterone acetate treatment (900 mg.) caused strong stimulation of libido and growth of the prostate. Inunction or injection were about equally effective, but effects rapidly subsided on discontinuance of treatment.—*H. G. O. Holck.*

RUBINSTEIN, H. S., H. D. SHAPIRO AND W. FREEMAN.

The treatment of morbid sex craving with the aid of testosterone propionate. *Am. J. Psychiat.* 97: 703. 1940.

Five women having excessive libido were treated with "large doses" (25 mg.) testosterone propionate. In each case the tension and inordinate erotic desire were promptly relieved. Two or 3 doses or less at 2 or 3-day intervals sufficed in 4 of the cases for considerable periods. The relief is ascribed to the action of the androgen upon the anterior pituitary.—*R.G.H.*

SIMONSON, E., W. M. KEARNS AND N. ENZER.

Effects of oral administration of methyl testosterone on fatigue in eunuchoids and castrates. *Endocrinology* 28: 506. 1941.

In 4 ♂ subjects with diminished production of sexual hormone (2 eunuchoids, 2 castrates) 4 weeks testosterone treatment resulted in: increase of muscular performance, *a*) in a type of dynamic work in the average of 68.5%; *b*) in a type of static work in the average of 41.1%; *c*) in

work with the finger-ergograph in the average of 45.4%. The absolute muscular strength was slightly increased. The recovery speed increased in static work and in finger-ergograph work. The maximum increase of pulse rate during dynamic work was diminished indicating more efficient circulatory system. The pulmonary ventilation was slightly decreased in static work and unchanged in dynamic work. The fusion frequency of flicker was increased thus pointing to an increased resistance of the central nervous system against fatigue.—*Authors' summary.*

VOIGHT, W. W.

Hypopituitary sterility improved by splitting the ovary. *Illinois M. J.* 79: 52. 1941.

In a case of infantile ovaries, tubes and uterus, due to pituitary hypofunction, the author attempted to obtain ovulation by means of estrogen and therapy by various pituitary substances, without result. The patient was a woman who was married 4 years without conceiving. Menses began at age 15, were regular and of 5 days' duration. Believing that the hard ovarian capsule prevented escape of the ovum, the ovary was split and the cut margins were sutured to the broad ligament. The operation was performed through the vaginal route. Normal conception occurred during the second cycle following operation, resulting in the birth of a normal infant at term.—*I.B.*

HYPOPHYSIS

BAUER, W., AND J. C. AUB.

Studies of calcium and phosphorus metabolism. XVI. The influence of the pituitary gland. *J. Clin. Investigation* 20:295. 1941.

Ca, P and N balance studies were made on 5 patients suffering from varying degrees of acromegaly. The Ca and P metabolism of acromegalics differed from that of normal individuals, being characterized by an increased urinary Ca and P excretion, in the presence of a normal serum concentration and a normal fecal excretion of Ca and P. This metabolic finding is not encountered in either hyperthyroidism or hyperparathyroidism. Since in hyperparathyroidism the increased urinary Ca and P excretions are associated with hypercalcemia and hypophosphatemia and since in hyperthyroidism the increased urinary excretion of Ca and P is accompanied by an increased fecal excretion of these substances, it is unlikely that the increased urinary Ca excretion of the acromegalic in the presence of normal serum values and normal fecal excretion of Ca and P is the result of stimulation of either the thyroid or the parathyroid glands by the pituitary. Roentgen ray therapy of the pituitary in 2 of the patients was followed by a reduced urinary Ca and P excretion in one.—*G.W.T.*

BOYD, E. M., AND R. W. DINGWALL.

The rate of thermal destruction of water balance principles in pituitary (posterior lobe) extract assayed by the Burn and Boyd-Mack methods. *J. Pharmacol. & Exper. Therap.* 71: 253. 1941.

Burn's assay method (delayed diuresis in hydrated rats) is compared to the Boyd-Mack assay method (water uptake of frogs injected with posterior lobe extract) when posterior lobe extracts are slowly destroyed by heat. The two methods give identical curves of destruction.—*C.P.*

LEVIN, L.

Quantitative precipitation of the urinary gonadotropin of normal men and women. *Endocrinology* 28: 378. 1941.

Recovery of gonadotropin from specimens of normal ♂ urine by tannic acid precipitation and by alcohol precipitation were compared. The extract of the initial alcohol precipitate was too toxic to permit assay of the small amounts of gonadotropin present (less than 30 mouse uterus units per 24-hour specimen). The alcohol extracts were consequently partially detoxified by dialysis, necessitating reconcentration, accomplished by acetone precipitation or by evaporation in a stream of air of the dialyzed solutions. Activity of the dialyzed, reconcentrated extracts of the alcohol precipitates was uniformly lower, by as much as 50%, than that of the corresponding tannic acid preparations. Investigation of the low yields obtained by alcohol precipitation showed that 10 to 15% of the activity remained in the insoluble residue of the alcohol precipitate. A further fraction, 25 to 30%, was possibly lost during the manipulations incident to dialysis and as much as 20% was lost during the air evaporation. The findings demonstrate the inadvisability of the avoidable manipulation when dealing with gonadotropin in amounts as small as those in normal urines, that the original claims for the quantitative precipitation by tannic acid were not unjustified, and that tannic acid was the most effective precipitant yet proposed for quantitative recovery of urinary gonadotropin of normal individuals.—*L. Levin.*

MOGENSEN, E.

Three cases of Simmonds' syndrome. With special reference to clinical diagnosis and treatment. *Acta med. Scandinav.* 105: 378. 1940.

A report is given of Simmonds' syndrome in 2 ♂ ♂ and 1 ♀ patient. All 3 cases showed the typical signs of the fully developed syndrome: loss of weight, asthenia, atrophy of the genital organs, changes in hair and skin, premature senility and low B.M.R. In the ♂ ♂ some improvement was obtained by treatment with gonadotropin from PU. In the 3rd patient these substances had no appreciable effect but treatment with estrin caused fair improvement. This patient had severe attacks of spontaneous hypoglycemia which could be controlled by frequent meals rich in carbohydrate.—*J.M.L.*

MUSSIO-FOURNIER, J. C., J. M. CERVINO AND O. CONTI.

The treatment of vitiligo by local injections of melanophore hormone. *Endocrinology* 28: 515. 1941.

The first case reported is that of a patient who was strikingly improved by the oral administration of fresh bovine hypophysis, an improvement which was maintained and increased through the use of local injections of melanophore hormone. The second case is that of a patient greatly benefited by the exclusive use of melanophore hormone.—*Author's abstract.*

PANCREAS

CUTTING, W. C., AND G. B. ROBSON.

Clinical trials with insulin-quinine mixtures by mouth in diabetics. *Endocrinology* 28: 375. 1941.

Seven of 10 patients with mild and severe forms of diabetes reacted beneficially when given variable doses of an insulin-quinine mixture by mouth. In some instances the mixture was given with alcohol. About ½ the patients showed the well-known side reactions of cinchonism in variable degree. Results are encouraging with respect to future possibilities of discovering more efficient and less objectionable agents than quinine for promoting gastrointestinal absorption of insulin. Meanwhile, the insulin-quinine mixtures used are not to be recommended for clinical use.—*Authors' conclusions.*

KRARUP, N. B.

Alkali treatment in diabetic coma with hyperazotemia and anuria. *Ugesk. f. laeger* 102: 27. 1940.

In a typical case of renal form of diabetic coma insulin failed to restore the patient's alkali reserve in several days, although other responses to insulin therapy were good. Anuria with rising blood urea developed. One liter of 1.3% isotonic sodium bicarbonate was given intravenously for 3 days. Alkali reserve rose and the patient gradually made complete recovery of kidney function. Deficiency of fixed base seems to be the cause of the anuria, and therapy with isotonic sodium bicarbonate intravenously according to the nonogram of Palmer and v. Slyke is indicated after determining the alkali reserve.—*H. G. O. Holck.*

MIRSKY, I. A., M. KORENBERG, N. NELSON AND W. E. NELSON.

The hepatic glycogen reserves in diabetes mellitus. *Endocrinolgoy* 28: 358. 1941.

Phlorhizin administration and the consequent glycosuria results in removal of circulating sugar. When the liver glycogen reserve is adequate the blood sugar remains relatively constant. When the glycogen reserve is inadequate the blood sugar level drops and ketosis may develop. Diabetic adults do not retain carbohydrate in their livers to the same degree as do normal adults, and removal of relatively small amounts of sugar from their blood stream results in further deprivation of liver glycogen with a consequent development of hypoglycemia and ketosis. Children do not retain carbohydrate to the same degree as do adults because of an apparent increased rate of glycogenolysis. This is true not only for diabetic children, but also for normal children and accounts for their greater susceptibility to ketosis and coma.—*From authors' summary.*

SISSON, W. R.

The neonatal problem in infants of diabetic mothers. *J.A.M.A.* 115: 2040. 1940.

In a consecutive series of 65 infants born of diabetic mothers, 57% were normal and 43% presented symptoms in the neonatal period. The mortality rate was 18%. Symptoms presented varied greatly and were caused by many conditions. Cerebral anoxia with involvement of the respiratory center appeared to be the cause of many of the symptoms. Infants of diabetic mothers showed high blood sugar levels. Hypoglycemia is a rare complication but may occur if insulin is given the mother shortly before delivery. The routine administration of parenteral dextrose immediately after birth is not indicated.—*From author's conclusions.*

SPIEGELMAN, A. R.

Influence of estrogen on the insulin requirement of the diabetic. *Am. J. M. Sc.* 200: 228. 1940.

Administration of 10,000 I.U. of estrogenic hormone twice weekly to a series of 9 diabetic women was associated with a diminution of their insulin requirement. The average daily requirement did not return to the pre-estrogen level even after estrogen had been discontinued for 3 months. The type of insulin used in control of the diabetics had no influence on results. In the premenopausal group the diminution in the insulin requirement associated with the administration of estrogen was greater and more sustained than in the postmenopausal group.—*Author's conclusions.*

WECHSLER, H. F., L. FARMER AND J. A. URBAN.

A case of insulin allergy simulating coronary occlusion. *J. Lab. & Clin. Med.* 26: 1090. 1941.

The injection of 20 U, and later 3 U of Iletin (Lilly) in a 65-year-old arteriosclerotic hypertensive diabetic patient gave rise to a syndrome strongly simulating coronary occlusion. The patient gave positive skin tests to all tested brands of insulin, including crystalline insulin. She did not react to pork, beef and lamb extracts. Passive transfer was attempted but the result was inconclusive as the normal test person also gave positive intradermal reactions in the untreated skin areas.—*G.W.T.*

PARATHYROIDS

ASHER, C.

The use of vitamin D preparations in the prevention and treatment of rickets. *Practitioner* 145: 61. 1940.

The proper prescribing of vitamin D for young children is discussed with the suggestion that the dose should always be stated in I.U. and not as so many teaspoonfuls of oil or other indefinite measures. A table is given showing the vitamin D content of the numerous available sources, with the ratio of vitamin D to vitamin A content of such products as cod liver oil, halibut liver oil, adexolin, radiostoleum and virol. It is considered that during the early years of life 3,000 to 1,500 I.U. vitamin D should be given daily from a source selected to suit individual taste and digestive capacity.—*From Child Development Abstracts.*

DOWNS, R. S., AND V. SCOTT.

Hyperparathyroidism with adenoma causing renal failure and secondary hyperparathyroidism. Report of a case. *Arch. Int. Med.* 67: 658. 1941.

A case with the following outstanding features is reported: hyperparathyroidism due to a parathyroid ade-

noma; diffuse renal calcinosis and renal insufficiency; values for serum Ca and inorganic P of 5.8 and 7.6 mg. %, respectively, shortly before death, and secondary hyperplasia of the 3 non-adenomatous parathyroid glands.—*I.B.*

HARRISON, H. E., AND H. C. HARRISON.

The renal excretion of inorganic phosphate in relation to the action of vitamin D and parathyroid hormone. *J. Clin. Investigation* 20: 47. 1941.

The phosphate excretion of ♀ dogs fed standardized diets was studied 18 to 20 hours after the last feeding. A solution of 0.1 molar sodium phosphate of approximately pH 7.4 was injected intravenously in a dose of 7 to 10 cc. per kg. of body weight, together with creatinine (0.3 gm. per kg.). Under standard conditions there was a limiting maximal rate of reabsorption of phosphate by the renal tubules which did not vary when the concentration of phosphate in the plasma was elevated by the administration of phosphate salts. The administration of vitamin D to 3 young dogs that had been fed previously a rachitogenic diet produced a marked increase in the maximal rate of reabsorption of phosphate by the renal tubules. This resulted in a rise of inorganic phosphate in the plasma. The effect could be demonstrated 24 hours after the administration of a single large dose (200,000 U) of vitamin D. The effect of parathyroid extract treatment on the tubular reabsorption of inorganic phosphate was opposite in nature to that of vitamin D. Following the injection of 2 to 6 cc. of parathyroid extract there was a considerable decrease in the rate of reabsorption of phosphate by the renal tubules which was followed by a reduction in the concentration of phosphate in the plasma.—*G.W.T.*

KOWALLIS, G. F.

Spontaneous parathyroid insufficiency. Report of a case. *Proc. Staff Meet. Mayo Clin.* 16: 129. 1941.

A case is reported of the development of convulsions in a married woman, aged 32 years that began 6 weeks after delivery. The last 3 months of pregnancy were accompanied by numbness and tingling of the hands and cramps in hands and legs. Serum Ca was 5.1 mg. per 100 cc. and phosphates 4.8 mg. The electroencephalogram showed atypical cerebral dysrhythmia. Treatment with dihydrotachysterol and calcium lactate brought about rapid clinical improvement and the Ca and P of the serum returned to normal.—*J.M.L.*

THYROID

CRAWFORD, T.

Carbohydrate tolerance in hypothyroidism and hyperthyroidism. *Arch. Dis. Child.* 15: 184. 1940.

Attempts were made to determine changes in carbohydrate tolerance of 6 hypothyroid and 2 hyperthyroid children. Two tests were employed to gauge carbohydrate tolerance; the oral dextrose and the intravenous dextrose tolerance tests. In cretinism the fasting blood sugar level was frequently subnormal and tended to rise under treatment with thyroid preparations. Results of the oral dextrose tests were irregular. Low curves were frequent, but normal and high curves also occurred. Intravenous dextrose tolerance tests revealed impairment of dextrose tolerance. This is in contrast to the usual assertion that tolerance to carbohydrate is increased in hypothyroidism. Under treatment all the curves tended to approach the normal; but if excessive dosage of thyroid was given impairment of tolerance reappeared in the form of high oral and delayed intravenous curves.—*From Child Development Abstracts.*

FAN, C.

Creatine and creatinine metabolism in hypothyroidism, with special reference to the limitations of using creatinine in the urine as a standard of basal energy metabolism. *J. Pediat.* 18: 57. 1941.

In three cases of hypothyroidism studied it was shown that the level of blood cholesterol gave a general indication of the therapeutic effect of thyroid, but did not serve as a reliable quantitative indicator of the B.M.R. The degree of creatinuria also did not parallel the B.M.R. level, either before or after thyroid therapy.—*Author's summary.*

MCCLENDON, J. F., AND W. C. FOSTER.

Thyroid hormone in blood and tissues in relation to basal metabolic rate. *Endocrinology* 28: 412. 1941.

With the exception of patients treated with certain I drugs other than KI and diiodotyrosine, all forms of I except thyroid hormone I can be extracted from the blood. Thyroid hormone I may be called thyroid I for brevity. Outside the thyroid, it seems probable that thyroid I is more or less equally distributed on the average. A study of the blood and B.M.R. of 373 patients and the study of tissues from numerous autopsies showed that for every microgram of thyroid I in 100 cc. of blood there is about 1 mg. of thyroxin in the body of a 65 kg. adult. The determination of thyroid I in the blood is a check on the reliability of the B.M.R. determination and is a substitute in case the B.M.R. cannot be determined. The use of elemental I (as in Lugol's solution), iodide of mercury or lipoids leads to error.—*Authors' summary.*

NIXON, N.

The treatment of Grave's disease in children. *J. Pediat.* 18: 71. 1941.

Although the etiology of Grave's disease is still unknown, Warthin's theory of a Grave's constitution seems tenable in view of pathologic and autopsy findings and is based upon the existence of a thymicolymphatic background in most instances of true exophthalmic goiter, with the thyroid changes but one manifestation of the general picture. Because the thyroid probably is not the primary pathogenic factor and because it plays a tremendously important part in the growth and development of the normal child, it seems advisable to treat Grave's disease in children on a conservative basis. Thyroidectomy should be performed only when no definite improvement is shown after a comparatively long period of treatment on a carefully planned and executed medical regime.—*Author's conclusions.*

PEREZ-FONTANA, V., AND H. CASTIGLIONI-ALONSO.

Hashimoto's disease. *An. Fac. Med. Montivideo Special Issue* 257. 1940.

Histological study of the thyroid gland in a case of goiter revealed both the lesions of the Riedel's struma and of the struma lymphomatosa (Hashimoto's disease) as well as transition types of lesions.—*J. E. Mackinnon.*

WILKINS, L.

Epiphyseal dysgenesis associated with hypothyroidism. *Am. J. Dis. Child.* 61: 13. 1941.

Epiphyseal dysgenesis associated with hypothyroidism is manifested in roentgenograms by the appearance of multiple irregular islets of ossification in the cartilages scattered over a large area. These enlarge and coalesce to form an irregular, spongy, porous or fluffy mass. All centers of endochondral ossification may be affected. The abnormality was found in 23 of 25 hypothyroid children of whom roentgenograms were made at frequent intervals after treatment was begun. It was found not only in cartilages which were ossified prior to thyroid treatment but also in those which began to ossify during treatment. Only those centers showed dysgenesis in which appearance of ossification had been delayed as a result of hypothyroidism. With continued treatment ossification took place normally in those centers which ordinarily would not have ossified at the age when therapy was begun. These observations suggest that in hypothyroidism a disturbance occurs in the cartilage in a stage just prior to the beginning of calcification.—*From author's summary.*

WILLIAMS, R. H., AND H. J. MORGAN.

Thyrotoxic osteoporosis. *New Internat. Clin.* II: 48. 1940.

Thyrotoxic osteoporosis has been observed in 7 cases at the Vanderbilt University Hospital. In 6, decalcification was marked and in 4 was associated with pathologic fractures. The presence of postural defects or the occurrence of muscle or joint pains in thyrotoxicosis may indicate the presence of osteoporosis. Experience thus far indicates that this complication of hyperthyroidism occurs chiefly in ♀ ♀ and in middle or late decades of life.—*Author's abstract.*

WINKELSTEIN, L. B.

The effect of thyroid on sterility in normal and hypothyroid females. *Am. J. Obst. & Gynec.* 40: 94. 1940.

Thyroid has a definite and valuable place in the treatment of ♀ sterility only if hypothyroidism is present. It is of little or no value where normal thyroid function exists.—*Author's abstract.*

WINKLER, A. W.

Hypometabolism following subtotal thyroidectomy. *Internat. Clin.* 1: 255. 1941.

This is a review of the incidence of post-thyroidectomy hypothyroidism with 7 illustrative case histories. A low B.M.R. following subtotal thyroidectomy for thyrotoxicosis occurs frequently and may be transient. Signs and symptoms of myxedema are rarely encountered. True temporary postoperative hypothyroidism is more common in recent years than in the past, possibly because of the current tendency to increased surgical radicalism. The majority of these patients with low B.M.R. have no symptoms of myxedema and do not respond favorably to thyroid medication. Both transient and persistent hypometabolism may occur with or without evidence of thyroid deficiency of varying degree. The great majority of postoperative hypometabolism cases present no proof of thyroid deficiency, but certain cases are indeed due to thyroid deficiency which should be treated accordingly. Response to thyroid substance is both the diagnostic and therapeutic test. In those cases tangibly due to thyroid deficiency the giving of thyroid substance for limited periods of time is the procedure of choice.—*I.B.*

ZONDEK, H.

On the problem of fetal function of the thyroid gland. *Acta med. Scandinav.* 103: 251. 1940.

A single case report of myxedema, ceasing to require thyroidin during pregnancy but relapsing after parturition. It is suggested the fetal thyroid during pregnancy supplied the maternal needs.—*J. F. Wilkinson.*